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(54) Title: AZA-CYCLIC COMPOUNDS AS MODULATORS OF ACETYLCHOLINE RECEPTORS

(57) Abstract: Compounds comprising an aza-cyclic portion and an aromatic portion linked via a sulphur atom are disclosed. The compounds disclosed are selective modulators of beta 4 subtype nicotinic acetylcholine receptors and are useful for the treatment of dysfunctions of the central and autonomic nervous systems.

AZA-CYCLIC COMPOUNDS AS MODULATORS OF ACETYLCHOLINE RECEPTORS

The present invention relates to compounds that modulate neurotransmission by promoting the release of neurotransmitters such as acetylcholine, dopamine and norepinephrine. More particularly, the present invention relates to thio-bridged aryl compounds that are capable of modulating acetylcholine receptors, methods of treatment which utilize such compounds and pharmaceutical compositions comprising such compounds.

- 10 Acetylcholine receptors modulate the release of neurotransmitters such as for example dopamine, norepinephrine, acetylcholine, and serotonin from different brain regions. By such action, acetylcholine receptors participate in the modulation of neuroendocrine function, respiration, mood, motor control and function, focus and attention, concentration, memory and cognition, and the mechanisms of substance abuse. Ligands
15 for acetylcholine receptors have been demonstrated to have effects on attention, cognition, appetite, substance abuse, memory, extrapyramidal function, cardiovascular function, pain, and gastrointestinal motility and function. The distribution of acetylcholine receptors that bind nicotine, i.e., nicotinic acetylcholine receptors, is widespread in the brain, including being found in the basal ganglia, limbic system, cerebral cortex and mid-
20 and hind-brain nuclei. In the periphery, their distribution includes being in muscle, autonomic ganglia, the gastrointestinal tract and the cardiovascular system.

Acetylcholine receptors have been shown to be decreased in the brains of patients suffering from Alzheimer's disease or Parkinson's disease, diseases associated with
25 dementia, motor dysfunction and cognitive impairment. Such correlations between acetylcholine receptors and nervous system disorders suggest that compounds that modulate acetylcholine receptors will have beneficial therapeutic effects for many human nervous system disorders. Thus, there is a continuing need for compounds that can modulate the activity of acetylcholine receptors.

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Nicotinic acetylcholine receptors (nAChRs) belong to the ligand gated ion channel family of neurotransmitter receptors. In neuronal and peripheral tissue, nAChRs possess a pentameric structure consisting of 5 protein subunits surrounding a central ion channel. Five neuromuscular subunits (α , β , γ , δ , ϵ), ten peripheral or neuronal α -subunits ($\alpha 1$ to $\alpha 10$), and three peripheral or neuronal β -subunits ($\beta 2$ to $\beta 4$) have been identified. These subunits combine to form pentameric receptors in three ways: first, with homomeric 5[α] stoichiometry, for example, $\alpha 7$ to $\alpha 9$; second, with heteromeric 2[α] 3 [β] stoichiometry, for example, combinations of $\alpha 1$ to $\alpha 6$ and $\beta 2$ to $\beta 4$ subunits; and third, the 2[α] 1 [β] 1 [δ] 1 [γ/ϵ] stoichiometry found in neuromuscular receptors.

10 Nicotine modulates multiple neuronal, peripheral and neuromuscular subtypes of nAChRs. While demonstrating beneficial effects in a number of neuronal diseases mediated by nAChRs, nicotine also demonstrates a number of undesirable side effects on cardiovascular, gastrointestinal and neuromuscular systems. It will be appreciated that there is a need for compounds that can selectively modulate a single or specific group of nAChRs.

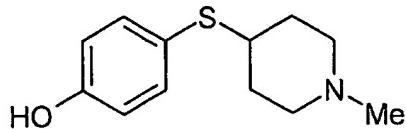
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It is desired to provide new compounds which selectively modulate the activity of acetylcholine receptors. In particular, it is desired to provide compounds that are capable 20 of acting as selective modulators, preferably agonists, of beta 4 subtype nicotinic acetylcholine receptors. It is also desirable to provide a method of treatment of dysfunctions of the central and peripheral nervous systems to treat, for example, 'dementia, cognitive and conduct disorders including attention deficit hyperactivity disorder, neurodegenerative disorders, including Alzheimers disease, Parkinson's disease 25 and other diseases in which degeneration leads to impaired functioning of the sensory or motor systems, extrapyramidal disorders associated with neuroleptic use, convulsive disorders, epilepsy, cardiovascular disorders, endocrine disorders, psychotic disorders including schizophrenia and related disorders, bipolar disease and obsessive-compulsive disorder, eating disorders, sleep-related disorders, affective disorders including 30 depression, anxiety, panic states and stress-related disorders, aggression, emesis, pain and hyperalgesic states of inflammatory and neuropathic origins, sleep and sexual disorders

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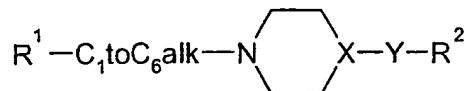
and alcohol and drug abuse or states associated with drug withdrawal including smoking cessation.

WO97/19059 discloses substituted aryl compounds capable of modulating acetylcholine
5 receptors. Specifically, it discloses the compound



Other compounds disclosed all possess a linker, usually methylene or ethylene, between
10 the S atom and either (or both) of the two ring systems shown above. WO99/32117
discloses similar compounds wherein the aryl moiety is replaced by a 2- or 4-pyridine
moiety. It would be desirable to provide alternative compounds to those disclosed in
WO97/19059 and WO99/32117. Preferably, such alternatives should exhibit one or more
15 of the following advantages: improved binding to nAChRs, greater modulation of
nAChRs, improved selectivity between different nAChRs and improved pharmacokinetic
properties (e.g. improved bioavailability).

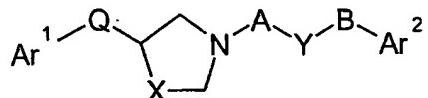
WO01/51469 discloses potent 5-HT_{2A} antagonists and their potential use for treating a
number of central nervous system disorders. The compounds disclosed are of the general
20 formula



wherein R¹ and R² maybe substituted or unsubstituted phenyl or substituted or
25 unsubstituted unsaturated heterocyclyl, Y maybe S when X is CH. Example 2 discloses a
number of substituted 4-(arylsulfanyl)-1-(arylalkyl)-piperidine compounds.

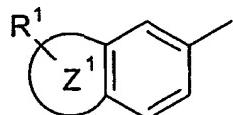
-4-

WO01/81303 discloses NMDA-receptor subtype selective blockers and their potential use for treating neurodegenerative disorders. The compounds are pyrrolidine and piperidine derivatives of the general formula



5

wherein Ar¹ may be pyridyl, phenyl or the group



10

wherein Z¹ is a five-membered heterocyclic ring, which contains one or two heteroatoms, selected from N or O and R¹ may be H or an oxo group. Ar² may be pyridyl or phenyl. Q may be S. X may be -(CH₂)_n. A-Y-B taken together may be unsubstituted or substituted alkylene. Intermediates useful for the synthesis of such derivatives are also disclosed.

15

Anpirtoline (2-chloro-6-(4-piperidinylthio)-pyridine) is discussed in numerous papers which describe its activity as an agonist at 5HT_{1B} and 5HT_{1D} receptors and as an antagonist at 5HT₃ receptors. Consequent utility of anpirtoline as an analgesic, anti-aggression treatment and as an anti-emetic is also disclosed.

20

EP-A-0149088 discloses certain substituted 2-(piperidyl-4-thio)-pyridine compounds including anpirtoline and structurally similar analogs thereof.

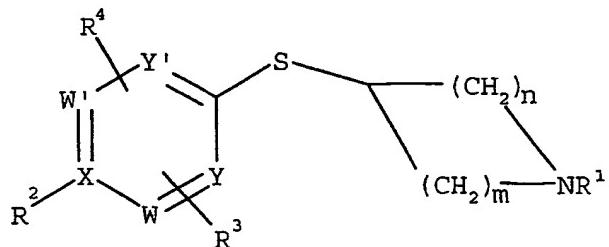
- Radl et al (Archiv der Pharmazie, Weinheim, Germany, 1999, 332(1), 13-18 and
25 Collection of Czechoslovak Chemical Communications 1999, 64(2), 363-376) disclose N-methyl,4-phenylthio-piperidine, derivatives of anpirtoline including 2-methyl,4-chloro-6-(4-pipiredinylthio)-pyridine and 4-(4-pipredinylthio)-6-chloro-pyridine and some deaza derivatives of anpirtoline including N-methyl,4-[(2-amino,5-chlorophenyl)thio]-

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piperidine, 4-[(2-chlorophenyl)thio]-piperidine, and N-methyl,4-[(3-chloro,4-aminophenyl)thio]-piperidine.

- EP-A-0160436 discloses certain phenyl-thiopiperidine compounds, including 4-phenylthio-piperidine, 3-phenylthio-piperidine and some deaza analogs of anpirtoline including 4-[(3-chlorophenyl)thio]-piperidine, 3-[(3-chlorophenyl)thio]-piperidine, 4-[(2-chlorophenyl)thio]-piperidine, 3-[(2-chlorophenyl)thio]-piperidine and 4-[(2,5-dichlorophenyl)thio]-piperidine as intermediates for the synthesis of compounds which are useful for the treatment or prophylaxis of cardiac arrhythmia.
- 10 EP-A-0304888 discloses alkylsulfonyl-aminophenyl-thiopiperidine compounds, including 4-[(4-methylsulfonylaminophenyl)thio]-piperidine, for use as medicaments for the treatment or prophylaxis of arrhythmia.
- 15 Wang et al (Yaoxue Xuebao, 2001, 36(4), 274-277) disclose 4-[(2,3-dimethoxyphenyl)thio]-piperidine as an intermediate in the preparation of 5-HT_{2A} selective ligands
- EP-A-0635505 discloses 4-[(4-methylsulfonylaminophenyl)thio]-piperidine and 4-[(4-acetamidophenyl)thio]-piperidine as intermediates in the synthesis of oxazolidinone derivatives as nervous system agents.

The present invention provides a method of treatment of a condition indicating treatment with a beta 4 subtype selective nicotinic acetylcholine receptor modulator, preferably an agonist, comprising administering an effective amount of a compound represented by Formula (I) or pharmaceutically acceptable salts thereof:



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(I)

wherein:

R¹ is -H,

5 C₁₋₁₂alkyl optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxyl, thiol, C₁₋₄alkoxy or C₁₋₄alkylthio, or aryl-C₁₋₄alkyl;

R² is -H,

-OH,

-C(O)-NH₂,

10 -NH₂,

-NH-Q-V-T, wherein

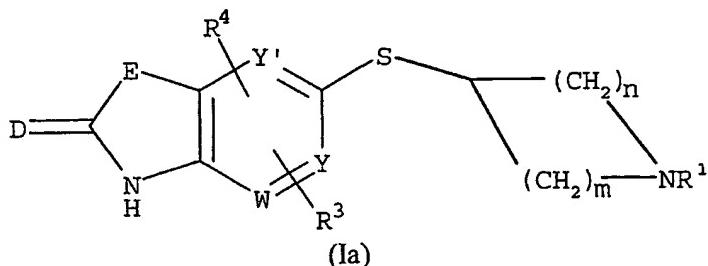
Q is -C(O)-, -C(O)-NH-, -C(O)O-, or -SO₂-;

V is H, aryl, aryl-C₁₋₁₂alkyl, diaryl-C₁₋₁₂alkyl, lactonyl, or C₁₋₁₈alkyl optionally substituted with halogen, hydroxyl, C₁₋₄alkoxy, -

15 C(O)OC₁₋₄alkyl, -OC(O)C₁₋₄alkyl, aryl-C₁₋₄alkoxy, aryloxy, or SO₂C₁₋₄alkyl; and

T is H, halogen, C₁₋₅alkyl, C₁₋₄alkoxy, nitro, aryl, aryl-C₁₋₄alkyl, or aryloxy unless V is H in which case T is absent; or

20 linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ia)



wherein D is O or S; and

25 E is O, S, NR⁵, C(R⁵)₂, O-CR⁵₂, NR⁵-CR⁵₂, NR⁵-CO, CR⁵₂-O, CR⁵₂-S(O)_r, CR⁵₂-NR⁵, CR⁵₂-CR⁵₂, CO-NR⁵, or CR⁵=CR⁵;

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unless X is N in which case R² is absent

R³ is H, halogen, C₁₋₄alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF₃, OC₁₋₄alkyl, aryloxy, arylC₁₋₄alkyl, arylC₁₋₄alkoxy, C₃₋₁₀cycloalkoxy, carboxy, carbonamido, -CO-, -CO₂H, -NH₂, NH-C₁₋₄alkyl, 5 aryl, hydroxy, -SO₂NH₂, -SO₂NHC₁₋₄alkyl, or -C₁₋₄alkyl-OH;

R⁴ is H, halogen, C₁₋₄alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF₃, OC₁₋₄alkyl, aryloxy, arylC₁₋₄alkyl, arylC₁₋₄alkoxy, C₃₋₁₀cycloalkoxy, carboxy, carbonamido, -CO-, -CO₂H, -NH₂, NH-C₁₋₄alkyl, aryl, hydroxy, -SO₂NH₂, -SO₂NHC₁₋₄alkyl, or -C₁₋₄alkyl-OH;

10 R⁵ is each independently H or C₁₋₄alkyl;

X is C or N;

W is C or N;

W' is C or N;

Y is C or N;

15 Y' is C or N;

provided that there are no more than two N atoms in the aryl ring;

m is 1, 2, or 3;

n is 1, 2, or 3; and

the sum of m and n is 2, 3, 4, 5, or 6;

20 provided that

when X, W, W', Y and Y' are all C, R³ and R⁴ are H and R¹ is selected from H, unsubstituted C₁₋₄alkyl and unsubstituted C₃₋₄cycloalkyl, R² may not be -OH;

and that

when one of X, Y and Y' is N, R³ and R⁴ are H and R¹ is selected from H, 25 unsubstituted C₁₋₄alkyl and unsubstituted C₃₋₄cycloalkyl, R² may not be H.

In a further embodiment of the present method, when X, W, W', Y and Y' are all C and R³ and R⁴ are H, R² may not be -OH and when one of X, Y and Y' is N and R³ and R⁴ are H, R² may not be H.

30

The present invention also provides a method of treatment of dysfunctions of the central and autonomic nervous systems comprising administering an effective amount of a

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compound represented by Formula (I) as described above or pharmaceutically acceptable salts thereof;

provided that

when X, W, W', Y and Y' are all C and R³ and R⁴ are H, R² may not be -OH;

5 and that

when one of X, Y and Y' is N and R³ and R⁴ are H, R² may not be H;

and that

when R² is H, OH or NH₂ and R³ and R⁴ are H, R¹ may not be aryl-C₁₋₄alkyl.

10 In a further embodiment of either of the methods disclosed above,

R¹ is -H, or

C₁₋₁₂alkyl optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxyl, thiol, C₁₋₄alkoxy or C₁₋₄alkylthio.

15 In a further embodiment of either of the methods disclosed above,

R² is -H,

-C(O)-NH₂,

-NH₂,

-NH-Q-V-T as defined above; or

20 linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ia) as defined above;

unless X is N in which case R² is absent.

In a further embodiment of either of the methods disclosed above,

25 R² is -C(O)-NH₂,

-NH-Q-V-T as defined above; or

linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ia) as defined above;

unless X is N in which case R² is absent.

30

In a further embodiment of either of the methods disclosed above,

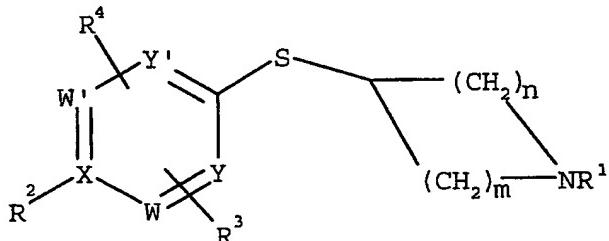
R² is -C(O)-NH₂,

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-NH-Q-V-T, wherein
 Q is -C(O)-NH-, or -C(O)O-;
 V is as defined above; and
 T is as defined above; or

linked back to the aromatic ring so as to form a fused bicyclic compound
 5 represented by Formula (Ia) as defined above;
 unless X is N in which case R² is absent.

Certain compounds falling within the scope of the methods described above are not known for use in therapy. Thus, the present invention provides for a compound of
 10 Formula (I) or pharmaceutically acceptable salts thereof for use in therapy:



(I)

wherein:

R¹ is -H,
 15 C₁₋₁₂alkyl optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxyl, thiol, C₁₋₄alkoxy or C₁₋₄alkylthio, or aryl-C₁₋₄alkyl;

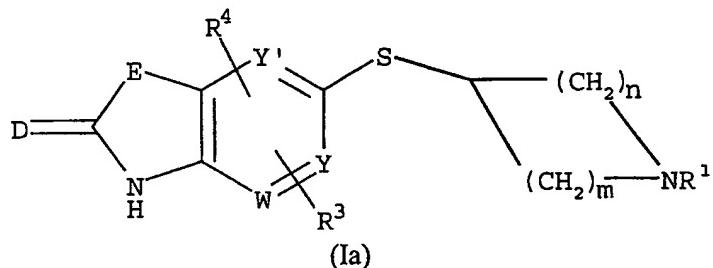
R² is -H,
 -OH,
 20 -C(O)-NH₂,
 -NH₂,
 -NH-Q-V-T, wherein Q is -C(O)-, -C(O)-NH-, -C(O)O-, or -SO₂-;
 V is H, aryl, aryl-C₁₋₁₂alkyl, diaryl-C₁₋₁₂alkyl, lactonyl, or C₁₋₁₈alkyl optionally substituted with halogen, hydroxyl, C₁₋₄alkoxy, -
 25

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C(O)OC₁₋₄alkyl, -OC(O)C₁₋₄alkyl, aryl-C₁₋₄alkoxy, aryloxy, or SO₂C₁₋₄alkyl; and
 T is H, halogen, C₁₋₅alkyl, C₁₋₄alkoxy, nitro, aryl, aryl-C₁₋₄alkyl, or aryloxy unless V is H
 in which case T is absent; or

5

linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ia)



10

wherein

D is O or S; and
 E is O, S, NR⁵, C(R⁵)₂, O-CR⁵₂, NR⁵-CR⁵₂, NR⁵-CO, CR⁵₂-O, CR⁵₂-S(O), CR⁵₂-NR⁵, CR⁵₂-CR⁵₂, CO-NR⁵, or CR⁵=CR⁵;

unless X is N in which case R² is absent

15

R³ is H, halogen, C₁₋₄alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF₃, OC₁₋₄alkyl, aryloxy, arylC₁₋₄alkyl, arylC₁₋₄alkoxy, C₃₋₁₀cycloalkoxy, carboxy, carbonamido, -CO-, -CO₂H, -NH₂, NH-C₁₋₄alkyl, aryl, hydroxy, -SO₂NH₂, -SO₂NHC₁₋₄alkyl, or -C₁₋₄alkyl-OH;

R⁴ is H, halogen, C₁₋₄alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF₃, OC₁₋₄alkyl, aryloxy, arylC₁₋₄alkyl, arylC₁₋₄alkoxy, C₃₋₁₀cycloalkoxy, carboxy, carbonamido, -CO-, -CO₂H, -NH₂, NH-C₁₋₄alkyl, aryl, hydroxy, -SO₂NH₂, -SO₂NHC₁₋₄alkyl, or -C₁₋₄alkyl-OH;

20

R⁵ is each independently H or C₁₋₄alkyl;

X is C or N;

25

W is C or N;

W' is C or N;

Y is C or N;

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Y' is C or N;

provided that there are no more than two N atoms in the aryl ring;

m is 1, 2, or 3;

n is 1, 2, or 3; and

5 the sum of m and n is 2, 3, 4, 5, or 6;

provided that

when X, W, W', Y and Y' are all C and R³ and R⁴ are H, R² may not be -OH;

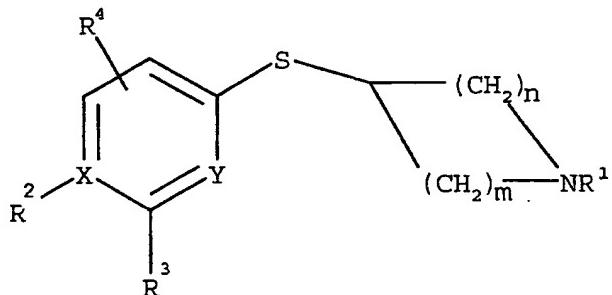
and that

when one of X, Y and Y' is N and R³ and R⁴ are H, R² may not be H;

10 and that

when R² is H, OH or NH₂ and R³ and R⁴ are H, R¹ may not be aryl-C₁₋₄alkyl;

and excluding compounds represented by Formula I' or pharmaceutically acceptable salts thereof:



15

(I')

wherein:

R¹, X, Y, m and n are as defined above

R² is -H,

-NH₂,

20 -NH-SO₂-V-T wherein V and T are as defined above;

unless X is N in which case R² is absent

R³ is H, halogen, C₁₋₄alkyl, -NH₂, NH-C₁₋₄alkyl, or hydroxy;

R⁴ is H, halogen, C₁₋₄alkyl, -NH₂, NH-C₁₋₄alkyl, or hydroxy.

25 In a further embodiment of the compounds disclosed above,

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R¹ is -H, or

C₁₋₁₂alkyl optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxyl, thiol, C₁₋₄alkoxy or C₁₋₄alkylthio.

5 In a further embodiment of the compounds disclosed above,

R² is -H,

-C(O)-NH₂,

-NH₂,

-NH-Q-V-T as defined above; or

10 linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ia) as defined above;

unless X is N in which case R² is absent.

In a further embodiment of the compounds disclosed above,

15 R² is -C(O)-NH₂,

-NH-Q-V-T as defined above; or

linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ia) as defined above;

unless X is N in which case R² is absent.

20

In a further embodiment of the compounds disclosed above,

R² is -C(O)-NH₂,

-NH-Q-V-T, wherein Q is -C(O)-NH-, or -C(O)O-;

V is as defined above; and

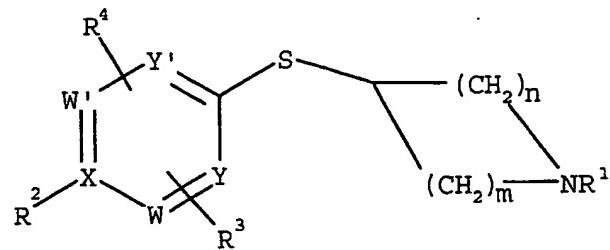
T is as defined above; or

linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ia) as defined above;

unless X is N in which case R² is absent.

30 The present invention also provides certain compounds which are novel. Accordingly, the present invention provides compounds represented by formula (I) or pharmaceutically acceptable salts thereof:

-13-



(I)

wherein:

R<sup>1</sup> is -H,

5 C₁₋₁₂alkyl optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxyl, thiol, C₁₋₄alkoxy or C₁₋₄alkylthio, or aryl-C₁₋₄alkyl;

R<sup>2</sup> is -H,

-OH,

10 -C(O)-NH<sub>2</sub>,

-NH<sub>2</sub>,

-NH-Q-V-T, wherein

Q is -C(O)-, -C(O)-NH-, -C(O)O-, or -SO<sub>2</sub>-;

V is H, aryl, aryl-C<sub>1-12</sub>alkyl, diaryl-C<sub>1-12</sub>alkyl, lactonyl, or C<sub>1-18</sub>alkyl optionally substituted with halogen, hydroxyl, C<sub>1-4</sub>alkoxy, -

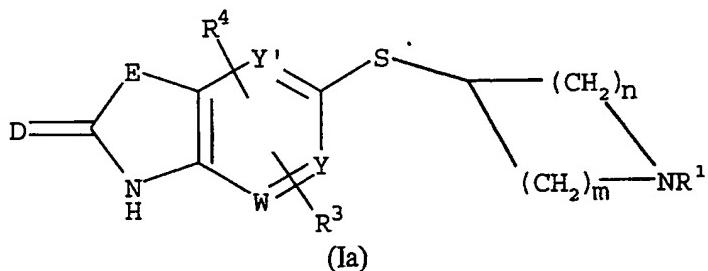
C(O)OC<sub>1-4</sub>alkyl, -OC(O)C<sub>1-4</sub>alkyl, aryl-C<sub>1-4</sub>alkoxy, aryloxy, or SO<sub>2</sub>C<sub>1-4</sub>alkyl; and

T is H, halogen, C<sub>1-5</sub>alkyl, C<sub>1-4</sub>alkoxy, nitro, aryl, aryl-C<sub>1-4</sub>alkyl, or aryloxy unless V is H in which case T is absent; or

15

20

linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ia)



wherein D is O or S; and
 E is O, S, NR⁵, C(R⁵)₂, O-CR⁵₂, NR⁵-CR⁵₂,
 5 NR⁵-CO, CR⁵₂-O, CR⁵₂-S(O)_n, CR⁵₂-NR⁵,
 CR⁵₂-CR⁵₂, CO-NR⁵, or CR⁵=CR⁵;

unless X is N in which case R² is absent

- R³ is H, halogen, C₁₋₄alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF₃, OC₁₋₄alkyl, aryloxy, arylC₁₋₄alkyl, arylC₁₋₄alkoxy, C₃₋₁₀cycloalkoxy, carboxy, carbonamido, -CO-, -CO₂H, -NH₂, NH-C₁₋₄alkyl, 10 aryl, hydroxy, -SO₂NH₂, -SO₂NHC₁₋₄alkyl, or -C₁₋₄alkyl-OH;
- R⁴ is H, halogen, C₁₋₄alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF₃, OC₁₋₄alkyl, aryloxy, arylC₁₋₄alkyl, arylC₁₋₄alkoxy, C₃₋₁₀cycloalkoxy, carboxy, carbonamido, -CO-, -CO₂H, -NH₂, NH-C₁₋₄alkyl, 15 aryl, hydroxy, -SO₂NH₂, -SO₂NHC₁₋₄alkyl, or -C₁₋₄alkyl-OH;
- R⁵ is each independently H or C₁₋₄alkyl;
- X is C or N;
- W is C or N;
- W' is C or N;
- Y is C or N;
- Y' is C or N;
- provided that there are no more than two N atoms in the aryl ring;
- m is 1, 2, or 3;
- n is 1, 2, or 3; and
- 25 the sum of m and n is 2, 3, 4, 5, or 6.

provided that

when X, W, W', Y and Y' are all C and R³ and R⁴ are H, R² may not be -OH;

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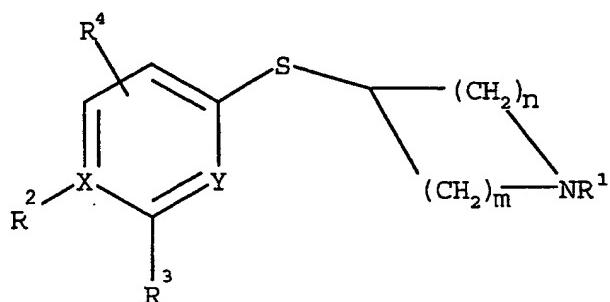
and that

when one of X, Y and Y' is N and R³ and R⁴ are H, R² may not be H;

and that

when R² is H, OH or NH₂ and R³ and R⁴ are H, R¹ may not be aryl-C1-4alkyl;

- 5 and excluding compounds represented by Formula I'' or pharmaceutically acceptable salts thereof:



(I'')

wherein:

10 R¹, X, Y, m and n are as defined above

R² is -H,

-NH₂,

-NH-Q-V-T, wherein Q is -C(O)- or -SO₂- and

V and T are as defined above;

15 unless X is N in which case R² is absent

R³ is H, halogen, C₁₋₄alkyl, OC₁₋₄alkyl, -NH₂, NH-C₁₋₄alkyl, or hydroxy;

R⁴ is H, halogen, C₁₋₄alkyl, OC₁₋₄alkyl, CO₂H, -NH₂, NH-C₁₋₄alkyl, or hydroxy.

In a further embodiment of the novel compounds disclosed above,

20 R¹ is -H, or

C₁₋₁₂alkyl optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxyl, thiol, C₁₋₄alkoxy or C₁₋₄alkylthio.

In a further embodiment of the novel compounds disclosed above,

25 R² is -H,

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- C(O)-NH₂,
- NH₂,
- NH-Q-V-T as defined above; or
- linked back to the aromatic ring so as to form a fused bicyclic compound
- 5 represented by Formula (Ia) as defined above;
- unless X is N in which case R² is absent.

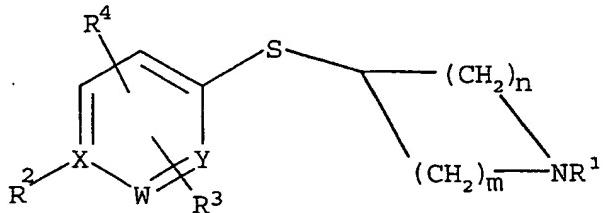
In a further embodiment of the novel compounds disclosed above,

- R² is -C(O)-NH₂,
- 10 -NH-Q-V-T as defined above; or
- linked back to the aromatic ring so as to form a fused bicyclic compound
- represented by Formula (Ia) as defined above;
- unless X is N in which case R² is absent.

- 15 In a further embodiment of the novel compounds disclosed above,

- R² is -C(O)-NH₂,
- NH-Q-V-T, wherein Q is -C(O)-NH-, or -C(O)O-;
- V is as defined above; and
- T is as defined above; or
- 20 linked back to the aromatic ring so as to form a fused bicyclic compound
- represented by Formula (Ia) as defined above;
- unless X is N in which case R² is absent.

- 25 In one embodiment, the present invention provides a sub-group of compounds (Group A)-
represented by formula (II) or pharmaceutically acceptable salts thereof:



(II)

wherein:

R¹ is -H, or

C₁₋₁₂alkyl optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxyl, thiol, C₁₋₄alkoxy or C₁₋₄alkylthio, or

5 aryl-C₁₋₄alkyl;

R² is -H,

-OH,

-C(O)-NH₂,

-NH₂,

10 -NH-Q-V-T, wherein Q is -C(O)-, -C(O)-NH-, -C(O)O-, or -SO₂-;

V is aryl, aryl-C₁₋₁₂alkyl, diaryl-C₁₋₁₂alkyl, lactonyl, or C₁₋₁₈alkyl optionally substituted with halogen, hydroxyl, C₁₋₄alkoxy, -

15 C(O)OC₁₋₄alkyl, -OC(O)C₁₋₄alkyl, aryl-C₁₋₄alkoxy, aryloxy, or SO₂C₁₋₄alkyl; and

T is H, halogen, aryl, aryl-C₁₋₄alkyl, or aryloxy;

unless X is N in which case R² is absent

R³ and R⁴ are each independently selected from H, halogen, C₁₋₄alkyl, cyano, CF₃,

20 OC₁₋₄alkyl, aryloxy, arylC₁₋₄alkoxy, C₃₋₁₀cycloalkoxy, carboxy, carbonamido, -CO-, -CO₂H, -NH₂, NH-C₁₋₄alkyl, aryl, hydroxy, -SO₂NH₂, -SO₂NHC₁₋₄alkyl, or -C₁₋₄alkyl-OH;

X is C or N;

W is C or N; provided that both X and Y are not N;

Y is C or N;

25 m is 1, 2, or 3;

n is 1, 2, or 3; and

the sum of m and n is 2, 3, 4, 5, or 6

Within Group A, R¹ is preferably -H; or C₁₋₁₂alkyl optionally substituted with 1, 2 or 3 groups independently selected from hydroxyl, thiol, C₁₋₄alkoxy or C₁₋₄alkylthio; or aryl-C₁₋₄alkyl.

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Within Group A, R¹ is more preferably H; C₁₋₆ alkyl optionally substituted with 1 or 2 hydroxyl groups; or aryl-C₁₋₄ alkyl. When R¹ is an aryl-C₁₋₄ alkyl group, examples of suitable groups are benzyl, p-methoxybenzyl, furanymethyl, imidazolymethyl, pyridinymethyl, thienymethyl, pyridylmethyl, N-hydroxypyridylmethyl or 5 thiazolymethyl.

Within Group A, R¹ is more preferably H, methyl, cyclopropylmethyl, 2-hydroxyethyl or isobutyl. When R¹ is one of these groups, greater potency is generally observed. More preferably, R¹ is a methyl group.

10 In one embodiment of Group A, R² is H. When R² is H, R³ is preferably carbonamido (-CONH₂) or -C₁₋₄alkyl-OH and R⁴ is H, C₁₋₄alkyl, CF₃, halogen or cyano (more preferably H, halogen or cyano). More preferably R³ is carbonamido (-CONH₂) or -C₁₋₄alkyl-OH and R⁴ is methyl, CF₃, Cl or cyano (more preferably Cl or cyano).

15 In another embodiment of Group A, R² is OH. When R² is OH, R³ and R⁴ are preferably H, C₁₋₄alkyl, CF₃, cyano or halogen (more preferably H, cyano or halogen). More preferably R³ is methyl, CF₃, Cl or cyano (more preferably Cl or cyano) attached to position Y when Y is C.

20 Generally, within Group A, when R² is of formula -NH-Q-V-T, T is preferably H and R³ and R⁴ are preferably H, methyl, CF₃, chloro- or cyano (more preferably H, chloro- or cyano).

25 In another embodiment of Group A, R² is of the formula -NH-SO₂-V-T, wherein V is aryl, -C₁₋₁₂alkyl or aryl-C₁₋₁₂alkyl. In this embodiment of the present invention R³ is preferably H, methyl, CF₃, Cl or cyano (more preferably H, Cl or cyano) and R⁴ is preferably H.

30 Within Group A, when R² is of formula -NH-SO₂-V-T, preferably V is selected from C₁₋₁₂ alkyl, phenyl, naphthyl, thienyl, oxazolyl, isoxazolyl, or phenyl (CH=CH)-, optionally substituted with 1, 2, 3 or 4 substituents selected from:

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- NO₂;
- halogen;
- CF₃;
- C₁₋₁₂ alkoxy;
- 5 C₁₋₁₂ alkylthio;
- C₁₋₁₂ alkyl;
- C₁₋₄ alkylsulfonyl;
- CN;
- OCF₃;
- 10 -C(O)OC₁₋₄ alkyl;
- OCH₂CF₃;
- NHC(O) C₁₋₄ alkyl.

Within Group A, when R² is of formula -NH-SO₂-V-T, preferably T is selected from H, or diazole, oxazole, isoxazole, phenyl or phenoxy, optionally substituted with 1, 2, 3 or 4 substituents selected from

- NO₂;
- halogen;
- CF₃;
- 20 C₁₋₁₂ alkoxy;
- C₁₋₁₂ alkylthio;
- C₁₋₁₂ alkyl;
- C₁₋₄ alkylsulfonyl;
- CN;
- 25 -OCF₃;
- C(O)OC₁₋₄ alkyl;
- OCH₂CF₃;
- NHC(O) C₁₋₄ alkyl.

30 Within Group A, when R² is of formula -NH-SO₂-V-T, V is more preferably selected from 3-chloro-4-methylphenyl, 3-chlorophenyl, 3-methoxyphenyl, 4-bromophenyl, 4-methoxyphenyl, 4-methylphenyl, naphthyl, 2,4,6-trimethylphenyl, phenyl(CH=CH)-, 4-chlorophenyl, 2-chlorophenyl, 2,5-dichlorothien-3-yl, 2,5,6-trimethyl-4-methoxyphenyl,

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- 4-methoxyphenyl, 2,3,4-trifluorophenyl, 3-cyanophenyl, 2-methoxycarbonylthien-3-yl or 4-pentylphenyl (even more preferably selected from 4-bromophenyl, 4-methoxyphenyl, 4-methylphenyl, naphthyl, 2,4,6-trimethylphenyl, phenyl(CH=CH)-, 4-chlorophenyl, 2-chlorophenyl, 2,5-dichlorothien-3-yl, 2,5,6-trimethyl-4-methoxyphenyl, 4-methoxyphenyl,
5 2,3,4-trifluorophenyl, 3-cyanophenyl, 2-methoxycarbonylthien-3-yl or 4-pentylphenyl) and T is preferably H.

In a further embodiment within Group A, when R² is of formula -NH-SO₂-V-T, T is preferably 2-chloro-5-nitrophenoxy and V is preferably phenyl.

- 10 In an alternative embodiment of Group A, R² is of formula -NH-C(O)-V-T wherein V is selected from

aryl;
aryl-C₁₋₁₂alkyl;
15 diaryl-C₁₋₁₂alkyl;
lactonyl; or
C₁₋₁₈alkyl optionally substituted with halogen, hydroxyl, C₁₋₄alkoxy, C(O)OC₁₋₄alkyl, OC(O)C₁₋₄alkyl, aryl-C₁₋₄alkoxy, aryloxy. In this embodiment of the present invention, R³ is preferably H, methyl, CF₃, Cl or cyano (more preferably H, 20 Cl or cyano) and R⁴ is H.

- When R² is of formula -NH-C(O)-V-T, preferably V is selected from C₁₋₁₂ alkyl, phenyl, phenyl-C₁₋₁₂ alkyl, diphenylmethyl, naphthyl, furanyl, thienyl, diazolyl, pyridinyl, thiazolyl, benzothienyl, fluorenyl, oxazolyl or isoxazolyl, optionally substituted with 1, 2, 25 3 or 4 substituents independently selected from

-NO₂;
halogen;
-CF₃;
C₁₋₁₂ alkoxy;
30 C₁₋₁₂ alkylthio;
C₁₋₁₂ alkyl;
C₁₋₄ alkylsulfonyl;

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-CN;
-OCF₃;
-C(O)O-C₁₋₄ alkyl;
-OCH₂CF₃.

5

More preferably V is C₁₋₁₂ alkyl.

When R² is of formula -NH-C(O)-V-T, preferably T is selected from

- H;
10 halogen; or
diazole, oxazole, isoxazole, phenyl, phenoxy or benzodioxanyl optionally substituted with 1, 2, 3 or 4 substituents selected from
-NO₂;
halogen;
15 -CF₃;
C₁₋₁₂ alkylthio;
C₁₋₁₂ alkoxy;
C₁₋₁₂ alkyl;
C₁₋₄ alkylsulfonyl;
20 -CN;
-OCF₃;
-C(O)O-C₁₋₄ alkyl.

More preferably T is H.

25 In an alternative embodiment of the present invention, R² is of formula -NH-C(O)N-V-T wherein V is selected from

- C₁₋₁₈ alkyl optionally substituted with halogen, hydroxyl, C₁₋₄ alkoxy,
C(O)OC₁₋₄ alkyl, OC(O)C₁₋₄ alkyl, aryl-C₁₋₄ alkoxy, aryloxy;
30 aryl; or
aryl-C₁₋₁₂ alkyl.

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When R² is of formula -NH-C(O)NH-V-T, preferably V is selected from phenyl, phenyl-C₁₋₁₂ alkyl or naphthyl optionally substituted with 1, 2, 3 or 4 substituents selected from

- NO₂;
- halogen;
- 5 -CF₃;
- C₁₋₁₂ alkylthio;
- C₁₋₁₂ alkoxy;
- C₁₋₁₂ alkyl;
- 10 C₁₋₄ alkylsulfonyl;
- CN;
- OCF₃;
- C(O)O-C₁₋₄ alkyl.

When R² is of formula -NH-C(O)NH-V-T, preferably T is H.

15 In an alternative embodiment of the present invention, R² is of formula -NH-C(O)O-V-T, wherein V is selected from

- C₁₋₁₈ alkyl optionally substituted with halogen, hydroxyl, C₁₋₄ alkoxy,
- C(O)OC₁₋₄ alkyl, OC(O)C₁₋₄ alkyl, aryl-C₁₋₄ alkoxy, aryloxy;
- 20 aryl; or
- aryl-C₁₋₁₂ alkyl.

When R² is of formula -NH-C(O)O-V-T, preferably V is selected from phenyl or phenyl-C₁₋₁₂ alkyl optionally substituted with 1, 2, 3 or 4 substituents selected from

- NO₂;
- halogen;
- 25 -CF₃;
- C₁₋₁₂ alkylthio;
- C₁₋₁₂ alkoxy;
- C₁₋₁₂ alkyl;
- 30 C₁₋₄ alkylsulfonyl;
- CN;
- OCF₃;
- C(O)O-C₁₋₄ alkyl; or

-OCH₂CF₃.

When R² is of formula -NH-C(O)O-V-T, preferably T is H.

- 5 In another embodiment, the present invention provides a further sub-group of compounds (Group B) represented by formula (I) or pharmaceutically acceptable salts thereof:

wherein R² is of formula -NH-C(O)-V-T

wherein V is H, C₁₋₆alkyl, C₃₋₆cycloalkyl, aryl or aryl-C₁₋₁₂alkyl; and

T is H, halogen, C₁₋₅alkyl, C₁₋₄alkoxy, nitro, aryl, aryl-C₁₋₄alkyl, or aryloxy

10 unless V is H in which case T is absent.

In a preferred embodiment within Group B, when V is H, C₁₋₆alkyl or C₃₋₆cycloalkyl, preferably T is H unless V is H in which case T is absent.

- 15 In another preferred embodiment within Group B, when V is aryl or aryl-C₁₋₁₂alkyl, preferably T is H, halogen, C₁₋₅alkyl, C₁₋₄alkoxy, nitro, aryl, aryl-C₁₋₄alkyl, or aryloxy. More preferably, V is phenyl, pyridyl, thienyl, thiazolyl, thiadiazolyl, or phenyl-C₁₋₆alkyl; and T is H, halogen, C₁₋₅alkyl, C₁₋₄alkoxy, nitro, aryl, aryl-C₁₋₄alkyl, or aryloxy.

- 20 In another embodiment, the present invention provides a further sub-group of compounds (Group C) represented by formula (I) or pharmaceutically acceptable salts thereof:

wherein

R¹ is -H,

C₁₋₁₂alkyl optionally substituted with 1, 2 or 3 groups independently

25 selected from halogen, hydroxyl, thiol, C₁₋₄alkoxy or C₁₋₄alkylthio, or aryl-C₁₋₄alkyl;

R² is -NH₂, or

-NH-Q-V-T, wherein Q is -C(O)-, -C(O)-NH-, -C(O)O-, or -SO₂-;

V is H, aryl, aryl-C₁₋₁₂alkyl, diaryl-C₁₋₁₂alkyl,

30 lactonyl, or C₁₋₁₈alkyl optionally substituted with halogen, hydroxyl, C₁₋₄alkoxy, -

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C(O)OC₁₋₄alkyl, -OC(O)C₁₋₄alkyl, aryl-C₁₋₄alkoxy, aryloxy, or SO₂C₁₋₄alkyl; and
T is H, halogen, aryl, aryl-C₁₋₄alkyl, or
aryloxy unless V is H in which case T is
absent,

5

R³ is H, halogen, C₁₋₄alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF₃, OC₁₋₄alkyl, aryloxy, arylC₁₋₄alkyl, arylC₁₋₄alkoxy, C₃₋₁₀cycloalkoxy, carboxy, carbonamido, -CO-NH-C₁₋₄alkyl, aryl, hydroxy, -SO₂NH₂, -SO₂NHC₁₋₄alkyl, or -C₁₋₄alkyl-OH;

10 R⁴ is H, halogen, C₁₋₄alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF₃, OC₁₋₄alkyl, aryloxy, arylC₁₋₄alkyl, arylC₁₋₄alkoxy, C₃₋₁₀cycloalkoxy, carboxy, carbonamido, -CO-NH-C₁₋₄alkyl, aryl, hydroxy, -SO₂NH₂, -SO₂NHC₁₋₄alkyl, or -C₁₋₄alkyl-OH;

X is C;

15 W is C or N;

W' is C or N;

Y is C or N;

Y' is C or N;

provided that there are not more than two N atoms in the aryl ring and provided
20 that at least one of W, W', Y or Y' is N;

m is 1, 2, or 3;

n is 1, 2, or 3; and

the sum of m and n is 2, 3, 4, 5, or 6; and

r is 0, 1 or 2.

25

In a preferred embodiment of the compounds of Group C only one of W, W', Y and Y' is N.

In one embodiment of the compounds of Group C

30 W is C;

W' is C;

Y' is C; and

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Y is N.

In another embodiment of the compounds of Group C

- W is N;
5 W' is C;
Y' is C; and
Y is C.

In another embodiment of the compounds of Group C, R² is -NH₂.

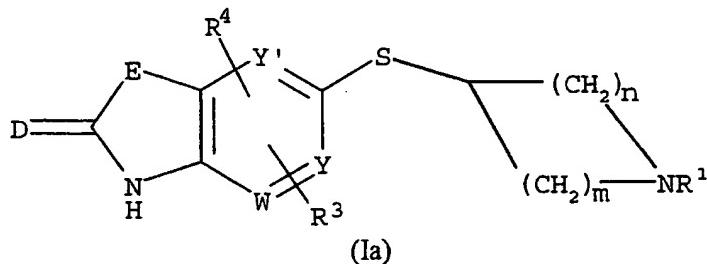
- 10 In another embodiment of the compounds of Group C
- R² is -NH-Q-V-T, wherein Q is -C(O)-, -C(O)-NH-, -C(O)O-, or -SO₂-; V is H, aryl, aryl-C₁₋₁₂alkyl, diaryl-C₁₋₁₂alkyl, lactonyl, or C₁₋₁₈alkyl optionally substituted with halogen, hydroxyl, C₁₋₄alkoxy, -C(O)OC₁₋₄alkyl, -OC(O)C₁₋₄alkyl, aryl-C₁₋₄alkoxy, aryloxy, or SO₂C₁₋₄alkyl; and T is H, halogen, aryl, aryl-C₁₋₄alkyl, or aryloxy unless V is H in which case T is absent.
- 15
- 20

Within Group C, when R² is -NH-Q-V-T, preferably Q is -SO₂- or -CO-.

- In another embodiment, the present invention provides a further sub-group of compounds
25 (Group F¹) represented by formula (I) or pharmaceutically acceptable salts thereof:
wherein:

- R¹ is -H,
C₁₋₁₂alkyl optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxyl, thiol, C₁₋₄alkoxy or C₁₋₄alkylthio, or
30 aryl-C₁₋₄alkyl;
- R² is linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ia)

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wherein D is O or S; and

5 E is O, S, NR⁵, or C(R⁵)₂,

R³ is H, halogen, C₁₋₄alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF₃, OC₁₋₄alkyl, aryloxy, arylC₁₋₄alkyl, arylC₁₋₄alkoxy, C₃₋₁₀cycloalkoxy, carboxy, carbonamido, -CO-NH-C₁₋₄alkyl, aryl, hydroxy, -SO₂NH₂, -SO₂NHC₁₋₄alkyl, or -C₁₋₄alkyl-OH;

10 R⁴ is H, halogen, C₁₋₄alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF₃, OC₁₋₄alkyl, aryloxy, arylC₁₋₄alkyl, arylC₁₋₄alkoxy, C₃₋₁₀cycloalkoxy, carboxy, carbonamido, -CO-NH-C₁₋₄alkyl, aryl, hydroxy, -SO₂NH₂, -SO₂NHC₁₋₄alkyl, or -C₁₋₄alkyl-OH;

R⁵ is each independently H or C₁₋₄alkyl;

15 X is C;

W is C or N;

W' is C;

Y is C or N;

Y' is C or N;

20 provided that there are no more than two N atoms in the aryl ring,

m is 1, 2, or 3;

n is 1, 2, or 3; and

the sum of m and n is 2, 3, 4, 5, or 6.

25 In one preferred embodiment of sub-group F¹, E is O or NR⁵.

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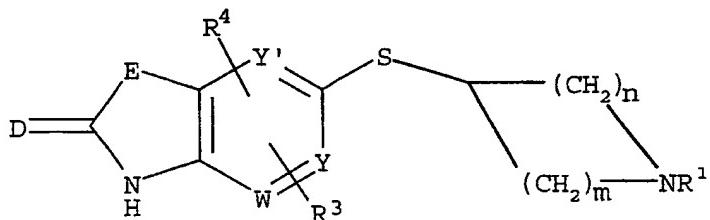
In another preferred embodiment of sub-group F¹, R⁵ is/are each independently H or C₁₋₄alkyl.

In another embodiment, the present invention provides a further sub-group of compounds
5 (Group F²) represented by formula (I) or pharmaceutically acceptable salts thereof:
wherein:

R¹ is -H,

C₁₋₁₂alkyl optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxyl, thiol, C₁₋₄alkoxy or C₁₋₄alkylthio, or
10 aryl-C₁₋₄alkyl;

R² is linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ia)



15

(Ia)

wherein D is O or S; and

E is O-CR⁵₂, NR⁵-CR⁵₂, NR⁵-CO, CR⁵₂-O, CR⁵₂-S(O)_n, CR⁵₂-NR⁵, CR⁵₂-CR⁵₂, CO-NR⁵, or CR⁵=CR⁵;

20

R³ is H, halogen, C₁₋₄alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF₃, OC₁₋₄alkyl, aryloxy, arylC₁₋₄alkyl, arylC₁₋₄alkoxy, C₃₋₁₀cycloalkoxy, carboxy, carbonamido, -CO-NH-C₁₋₄alkyl, aryl, hydroxy, -SO₂NH₂, -SO₂NHC₁₋₄alkyl, or -C₁₋₄alkyl-OH;

25

R⁴ is H, halogen, C₁₋₄alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF₃, OC₁₋₄alkyl, aryloxy, arylC₁₋₄alkyl, arylC₁₋₄alkoxy, C₃₋₁₀cycloalkoxy, carboxy, carbonamido, -CO-NH-C₁₋₄alkyl, aryl, hydroxy, -SO₂NH₂, -SO₂NHC₁₋₄alkyl, or -C₁₋₄alkyl-OH;

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R^5 is cycloalkoxy , carboxy , carbonamido , $-\text{CO-NH-C}_1\text{-4alkyl}$, aryl , hydroxy , -

$-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{NHC}_1\text{-4alkyl}$, or $-\text{C}_1\text{-4alkyl-OH}$;

R^5 is each independently H , $\text{C}_1\text{-4alkyl}$;

X is C ;

5 W is C or N ;

W' is C ;

Y is C or N ;

Y' is C or N ;

provided that there are no more than two N atoms in the aryl ring;

10 m is 1, 2, or 3;

n is 1, 2, or 3; and

the sum of m and n is 2, 3, 4, 5, or 6.

In one preferred embodiment of sub-group F^2 , E is O-CR^5_2 , $\text{NR}^5\text{-CR}^5_2$, $\text{NR}^5\text{-CO}$, CR^5_2 ,
15 CR^5_2 , or $\text{CR}^5=\text{CR}^5$. More preferably, E is O-CR^5_2 , $\text{NR}^5\text{-CO}$, or $\text{CR}^5=\text{CR}^5$.

In another preferred embodiment of sub-group F^2 , R^5 is/are each independently H or $\text{C}_1\text{-4alkyl}$.

20 Within Group A, m is preferably 2 and n is 1, 2 or 3. More preferably, m is 2 and n is 3.

Within Group A, X , Y and W are preferably C .

For all embodiments of the present invention, R^1 is preferably H or $\text{C}_{1-3}\text{alkyl}$, more
25 preferably methyl.

For all embodiments of the present invention, the sum of m , n , o and p is preferably 4.

More preferably, m and n are 2.

30 For all embodiments of the present invention it is preferred that m and n are 2 and R^1 is H or $\text{C}_{1-3}\text{alkyl}$.

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For all embodiments of the present invention, R³ is preferably H, halogen, C₁₋₄alkyl, cyano, CF₃, or OC₁₋₄alkyl, and R⁴ is preferably H, halogen, C₁₋₄alkyl, cyano, CF₃, or OC₁₋₄alkyl.

- 5 For all embodiments of the present invention, one or both of R³ and R⁴ is/are not H and is/are preferably positioned ortho to the S linker moiety.

For all embodiments of the present invention, one or both of R³ and R⁴ is/are halogen, C₁₋₄alkyl, cyano, CF₃, or OC₁₋₄alkyl, more preferably halogen, cyano, or C₁₋₄alkyl, most 10 preferably halogen, positioned ortho to the S linker moiety.

As used herein, the term "alkyl" means a branched or unbranched, cyclic and/or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl), monovalent or divalent hydrocarbyl radical. Examples of branched alkyl groups are isopropyl, isobutyl, tert-butyl etc.

- 15 Examples of cyclic alkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl etc. Examples of groups containing both cyclic and acyclic alkyl moieties are cyclopropylmethyl, cyclohexylpropyl, adamantylethyl etc.

As used herein, the term "aryl" means a C₃ to C₂₆, preferably C₃ to C₁₂ aromatic or 20 heteroaromatic group which may, optionally, be substituted with one or more substituents. Aryl substituents are preferably selected from C₁ to C₁₂ alkyl (preferably C₁ to C₆ alkyl), C₁ to C₁₂ alkoxy (preferably C₁ to C₆ alkoxy), thio, C₁ to C₁₂ alkylthio (preferably C₁ to C₆ alkylthio), carboxy, carboxy(C₁ to C₆)alkyl, formyl, C₁ to C₆ alkylcarbonyl, C₁ to C₆ alkylsulfonyl, C₁ to C₆ alkylcarbonylalkoxy, nitro, trihalomethyl, trihalo(C₁ to C₆ alkoxy), 25 trihalomethoxy, trihalomethyl(C₁ to C₆ alkyl), hydroxy, hydroxy(C₁ to C₆)alkyl, (C₁ to C₆ alkoxy)carbonyl, amino, C₁ to C₆ alkylamino, di(C₁ to C₆ alkyl)amino, aminocarboxy, C₁ to C₆ alkylaminocarboxy, di(C₁ to C₆ alkyl)aminocarboxy, aminocarboxy(C₁ to C₆)alkyl, C₁ to C₆ alkylaminocarboxy(C₁ to C₆)alkyl, di(C₁ to C₆ alkyl)aminocarboxy(C₁ to C₆)alkyl, C₁ to C₆ alkylcarbonylamino, C₁ to C₆ alkylcarbonyl(C₁ to C₆ alkyl)amino, halo, 30 C₁ to C₆ alkylhalo, sulphamoyl, tetrazolyl and cyano.

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- Examples of aromatic groups are phenyl, naphthyl, fluorenyl, thiaryl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, diazolyl, triazolyl, tetrazolyl, benzothiazolyl, benzimidazolyl, pyrrolinyl, imidazolinyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, thianaphthyl, benzofuranyl, 5 isobenzofuranyl, benzothienyl, isobenzothienyl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, azabenzimidazolyl, carbazolyl benzopyranyl, coumarinyl, isocoumarinyl, quinolinyl, isoquinolinyl, quinazolinyl, benzoxazinyl, quinoxalinyl, chromenyl, chromanyl, isochromanyl, phthalazinyl, benzodioxolyl, benzodioxanyl, cinnolinyl and carbolinyl.
- 10 Terms such as "aryl-C₁₋₁₂ alkyl group" include groups such as benzyl, 4-chlorobenzyl, phenylpropyl, thienylethyl etc. Further, the alkyl moiety in, for example, aryl-C₁₋₁₂ alkyl groups may optionally be substituted with 1, 2 or 3 substituents selected from halogen, hydroxyl, C₁₋₄ alkoxy or C₁₋₄ alkylthio.
- 15 As used herein the term "lactonyl" means any C₁₋₁₈ cyclic ester. The lactonyl group may be monocyclic or polycyclic.

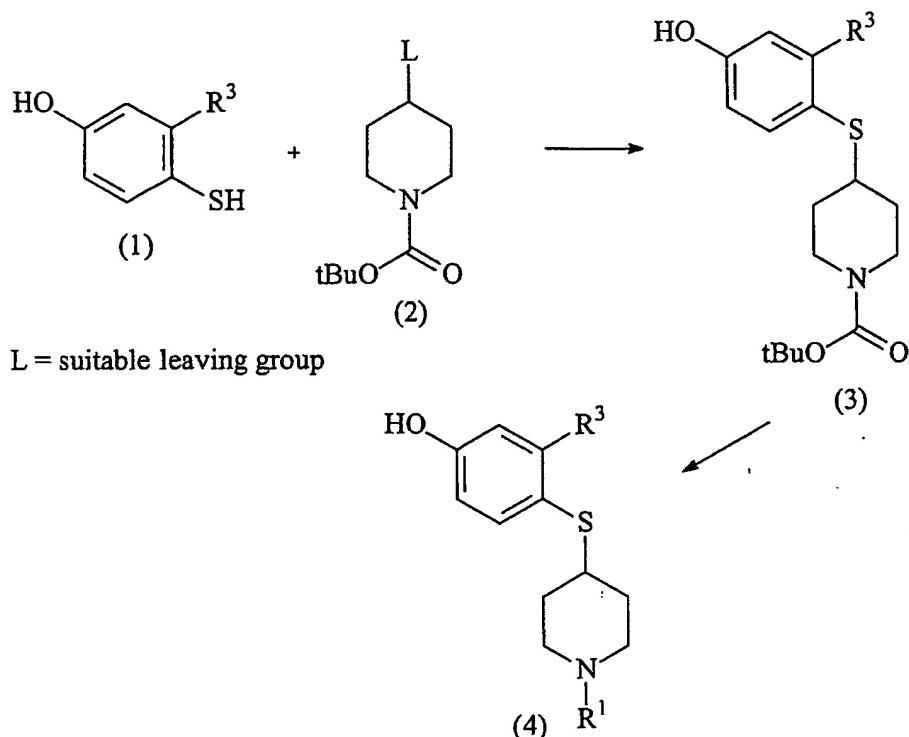
As used herein, the terms "halogen" or "halo" refer to any one of F, Cl, Br or I.

20 Compounds of Group A wherein
 $R^2 = OH$; and
 $R^3 = methyl, CF_3, \text{halogen or H};$
may be prepared by a procedure exemplified in Reaction Scheme 1.

25 While Reaction Scheme 1 exemplifies compounds of the present invention wherein m = n = 2, it will be readily apparent to the skilled person that the same procedures may be applied to other ring sizes (i.e. when the sum of m and n is 2, 3, 5 or 6).

30

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Reaction Scheme 1

- Thiophenol (1) [commercial or prepared according to Kita Y.; Takeda, Y.; Okuno, T.; Egi, M.; Ito, K.; Kawaguchi, K; Akai, S. *Chem. Pharm. Bull.* 1997, 45(12), 1887-1890 or Zheng, J.; Hanzlik, R. P. *Drug Metab. Dispos.* 1992, 20(5), 688-694], is coupled with carbamate (2) by displacement of the leaving group L. Suitable leaving groups will be readily apparent to the person skilled in the art. Typical leaving groups include iodo, chloro, bromo, mesyl or tosyl. The coupling reaction is preferably performed in a dipolar solvent such as methanol, THF or DMF. More preferably, the coupling reaction is performed in a 50/50 mixture of THF and DMF. The coupling reaction is preferably promoted by a suitable base such as potassium hydroxide, sodium hydride, sodium ethoxide, potassium carbonate or DBU. More preferably, the coupling reaction is performed in the presence of potassium carbonate or sodium hydride. Typically the coupling reaction may be carried out over a temperature range of from -78 to 150°C. Preferably, the reaction is carried out at a temperature in the range of from room temperature to 70°C. Reaction times for the coupling reaction are typically from 10 minutes to 24 hours. Preferred reaction times are in the range of 30 minutes to 12 hours.

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Thioether (3) is subsequently converted into compounds of the present invention corresponding to the thioether of formula (4). When R¹ is methyl, compounds of formula (4) may be prepared by reduction using, for example, lithium aluminium hydride. When R¹ is other than methyl, compounds of formula (4) may be prepared by deprotection of the carbamate group (usually under acidic conditions) followed by reaction with a suitable aldehyde or allyl halide.

Reduction with lithium aluminium hydride is typically carried out in ether or THF (preferably THF). Preferably, the reduction is carried out at room temperature. Reaction times vary from 10 minutes to up to several days. Preferred reaction times are in the range of 12 to 48 hours.

Alternatively, when R¹ is other than methyl, the carbamate derivative (3) is deprotected under standard conditions. Typical carbamate deprotection conditions involve using either protic acids (e.g. trifluoroacetic acid, HCl, HBr) or Lewis acids (e.g. acid chlorides/bromides, tri(m)ethylsilyl triflate). The solvent used is typically water, dichloromethane, dioxane, THF or ether. Preferably, an acid chloride in dioxane is used when the protecting group is *tert*-butyl carbamate (Boc). Preferably, HBr in water is used when the protecting group is ethyl carbamate. Preferably, deprotection is carried out at room temperature (in the case of Boc-deprotection) or at reflux (in the case of ethyl carbamate).

Once a free amine has been realised following deprotection, procedures for introducing various R¹ groups (wherein R¹ is optionally substituted C₁₋₁₂ alkyl or aryl-C₁₋₄ alkyl) will be readily apparent to the skilled person. Generally, displacement of an alkyl halide (or reductive alkylation with an aldehyde) furnishes the desired tertiary amine (4).

Compounds of Group A wherein:

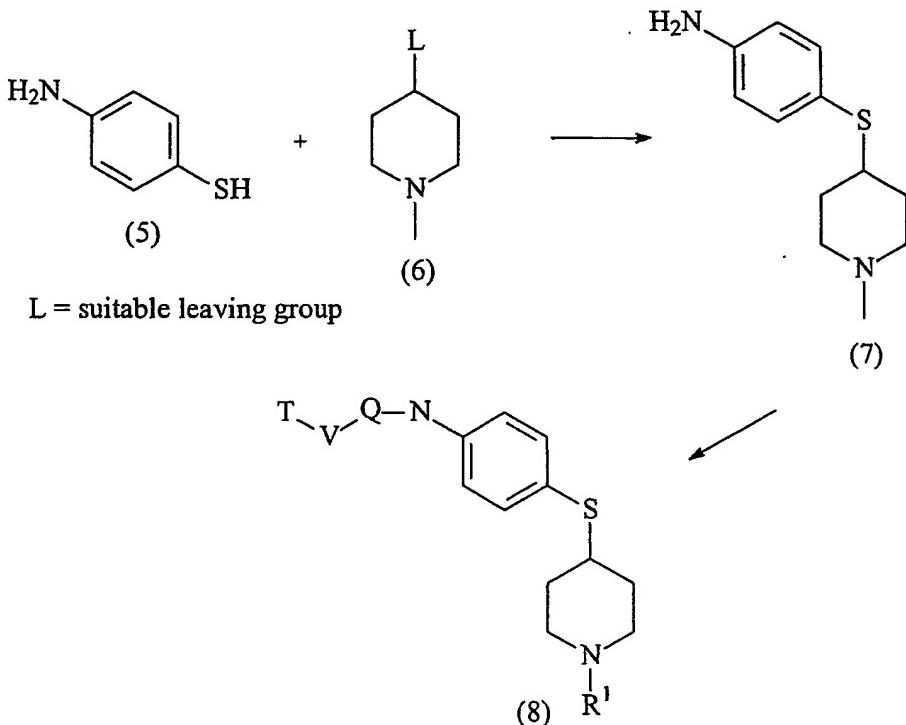
R¹ = methyl;
R² = -NH₂ or -NH-Q-V-T; and
R³ = H

May be prepared by a procedure exemplified in Reaction Scheme 2.

While Reaction Scheme 2 exemplifies compounds of the present invention wherein $m = n = 2$, it will be readily apparent to the skilled person that the same procedures may be applied to other ring sizes (i.e. when the sum of m and n is 2, 3, 5 or 6).

5

Reaction Scheme 2



Commercially available 4-aminothiophenol (5) is coupled with amine (6) by displacement of a suitable leaving group L, as outlined above in Reaction Scheme 1. The resultant thioether bridged compound (7) is a key intermediate in the synthesis of compounds of the present invention. It will be readily apparent to the person skilled in the art that various R² groups of general type -NH-Q-V-T may be prepared from compound (7) by standard procedures known in the art. For example, when:

- 15 (a) Q is $\text{-SO}_2\text{-}$, by coupling with a compound of general formula T-V-SO₂-L';
 (b) Q is -CO- , by coupling with a compound of general formula T-V-CO-L';
 (c) Q is -NH-C(O)- , by coupling with a compound of general formula T-V-N=C=O;

(d) Q is $-OC(O)-$, by coupling with a compound of general formula T-V-OC(O)-L'

wherein L' is any suitable leaving group, such as Cl, Br or I.

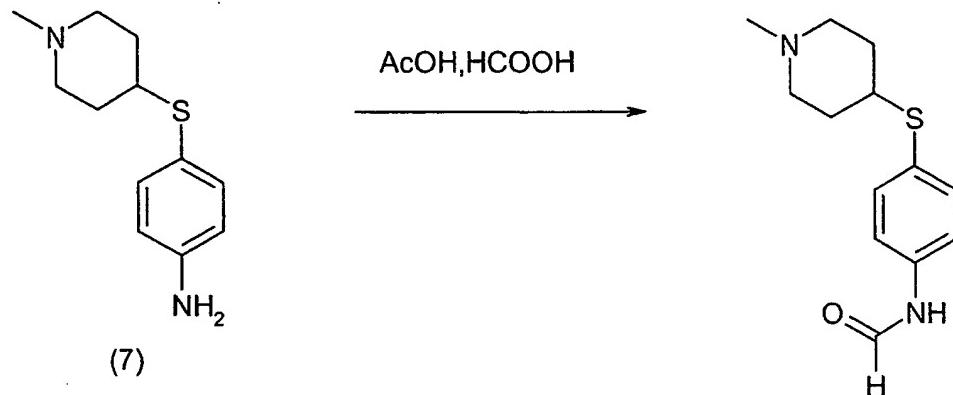
- 5 Typically, the coupling reaction which affords compounds of formula (8) is performed in pyridine or an aprotic solvent such as dichloromethane in the presence of a base such as pyridine, triethylamine or diisopropylamine. Preferably, the coupling is performed at room temperature with reaction times varying from 10 minutes to 24 hours, preferably 30 minutes to 12 hours.

10

Compounds of Group B wherein V is H may be prepared by a procedure exemplified in Reaction Scheme 3.

- While Reaction Scheme 3 exemplifies compounds of the present invention wherein m = n
 15 = 2, it will be readily apparent to the skilled person that the same procedures may be applied to other ring sizes (i.e. when the sum of m and n is 2, 3, 5 or 6).

Reaction Scheme 3



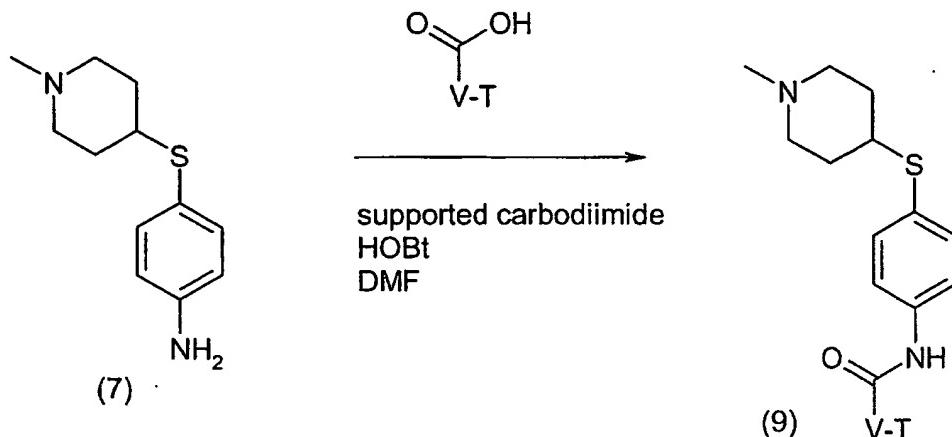
- 20 A mixture of acetic acid and formic acid is heated under reflux for about 2 hours. To this is added the thioether bridged compound (7) (prepared according to Scheme 2 above) and heating continues for about 1.5 hours. The crude mixture may be purified by elution on an SCX cartridge followed by flash chromatography.

Compounds of Group B wherein V is C₁₋₆alkyl, C₃₋₆cycloalkyl, aryl or aryl-C₁₋₁₂alkyl may be prepared by a procedure exemplified in Reaction Scheme 4.

- 5 While Reaction Scheme 4 exemplifies compounds of the present invention wherein $m = n = 2$, it will be readily apparent to the skilled person that the same procedures may be applied to other ring sizes (i.e. when the sum of m and n is 2, 3, 5 or 6).

Reaction Scheme 4

10



A mixture of the thioether bridged compound (7) (prepared according to Scheme 2 above), T-V-CO₂H, 1-hydroxybenzotriazole and carbodiimide resin in DMF is stirred at room temperature for about 3 days. The mixture is filtered then passed through an SCX cartridge to provide the product (9).

Compounds of Group C wherein R² is NH₂ may be prepared by a procedure exemplified in Reaction Scheme 5.

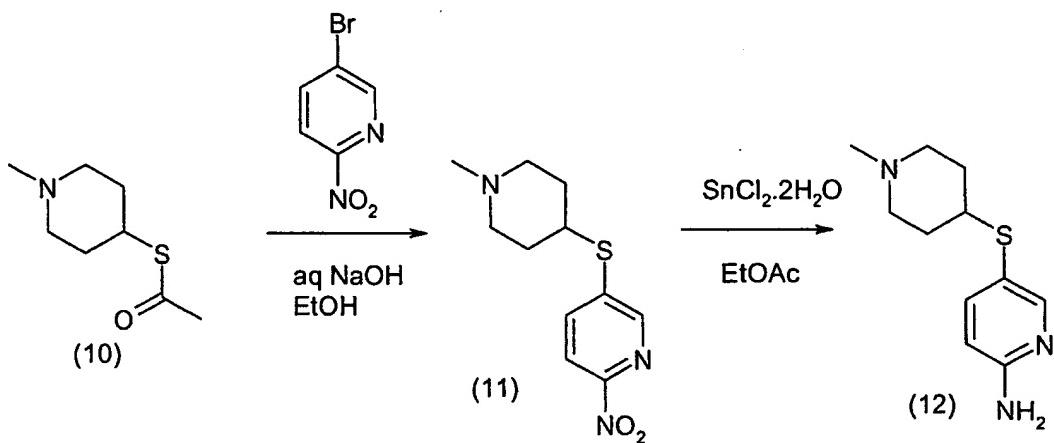
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While Reaction Scheme 5 exemplifies compounds of the present invention wherein $m = n = 2$, and W is N, it will be readily apparent to the skilled person that the same procedures may be applied to other ring sizes (i.e. when the sum of m and n is 2, 3, 5 or 6) or where Y is N.

5

Reaction Scheme 5



Step 1:

10 A mixture of the ethanethioate (10) and 2-nitro-5-bromopyridine in ethanol and aqueous sodium hydroxide is stirred at room temperature for about 18hours. The mixture is applied directly to an SCX cartridge and eluted to yield the crude product which may be purified by preparative LC-MS to provide the nitro-pyridinyl-thio-azacyclo compound (11).

15 **Step 2:**

A mixture of the nitro-pyridinyl-thio-azacyclo compound (11) and tin (II) chloride dihydrate in ethyl acetate is heated under reflux for about 4 days and then worked up by quenching with aqueous sodium hydrogen carbonate solution to provide the aminopyridine product (12). Step 2 may also be achieved by Pd/C catalysed H₂ reduction

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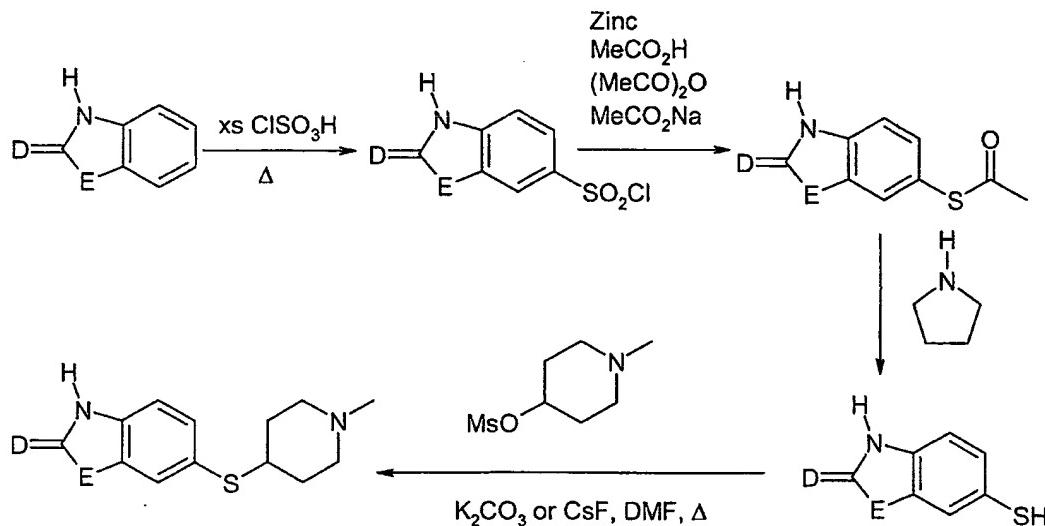
It will be readily apparent to the person skilled in the art that compounds of Group C wherein R² is -NH-Q-V-T may be prepared from compound (12) by standard procedures known in the art. For example, when:

- (e) Q is $\text{-SO}_2\text{-}$, by coupling with a compound of general formula T-V-SO₂-L';
 (f) Q is -CO- , by coupling with a compound of general formula T-V-CO-L';
 (g) Q is -NH-C(O)- , by coupling with a compound of general formula T-V-N=C=O;
 5 (h) Q is -OC(O)- , by coupling with a compound of general formula T-V-OC(O)-L'

wherein L' is any suitable leaving group, such as Cl, Br, or I.

Compounds of Group F¹ and F² may be prepared by procedures exemplified in Reaction Schemes 6 to 9. While the Schemes exemplify compounds of the present invention wherein m = n = 2, it will be readily apparent to the skilled person that the same procedures may be applied to other ring sizes (i.e. when the sum of m and n is 2, 3, 5 or 6).

15 Reaction Scheme 6



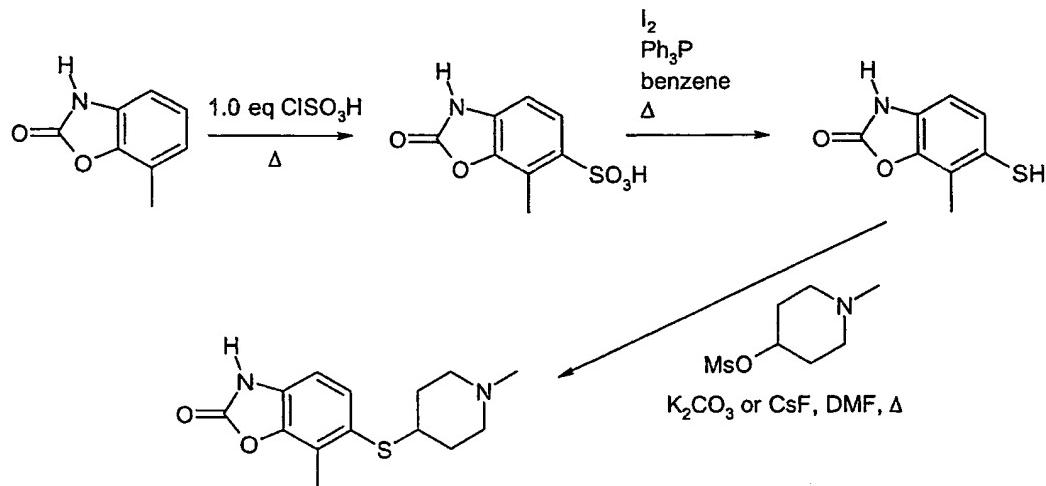
Unsubstituted precursors to compounds of group F¹ and F² (wherein R³ = H, R⁴ = H, D = O or S and E = O, S, NH, O-CR⁵₂, NR⁵-CR⁵₂, NR⁵-CO, CR⁵₂-O, CR⁵₂-S, CR⁵₂-NR⁵, CR⁵₂-CR⁵₂, CO-NR⁵, or CR⁵=CR⁵) may be treated with excess chlorosulphonic acid to 20 selectively introduce a chlorosulphonyl group para to the N-H. The chlorosulphonic acid may be used neat or in a solvent such as chloroform or dichloromethane at a temperature

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between 0 and 100 °C. Reduction to the acetylthio compound may be effected with zinc, acetic anhydride and acetic acid at a temperature between 0°C and ambient temperature. Removal of the acetyl group may be effected by a secondary amine such as pyrrolidine and subsequent alkylation of the free thiol with an appropriate mesylate may be mediated 5 by a base such as potassium carbonate or cesium fluoride in an aprotic solvent such as dimethylformamide. This reaction is performed between ambient temperature and 100°C.

An alternative route to aryl thiols is shown in scheme 7 for D = E = O and R³ = Me. This utilises 1 equivalent of chlorosulphonic acid at 0 °C and ambient temperature to give a 10 sulphonic acid derivative which may be reduced directly to a thiol using iodine and triphenylphosphine in a solvent such as benzene at reflux under Dean and Stark conditions.

Reaction Scheme 7

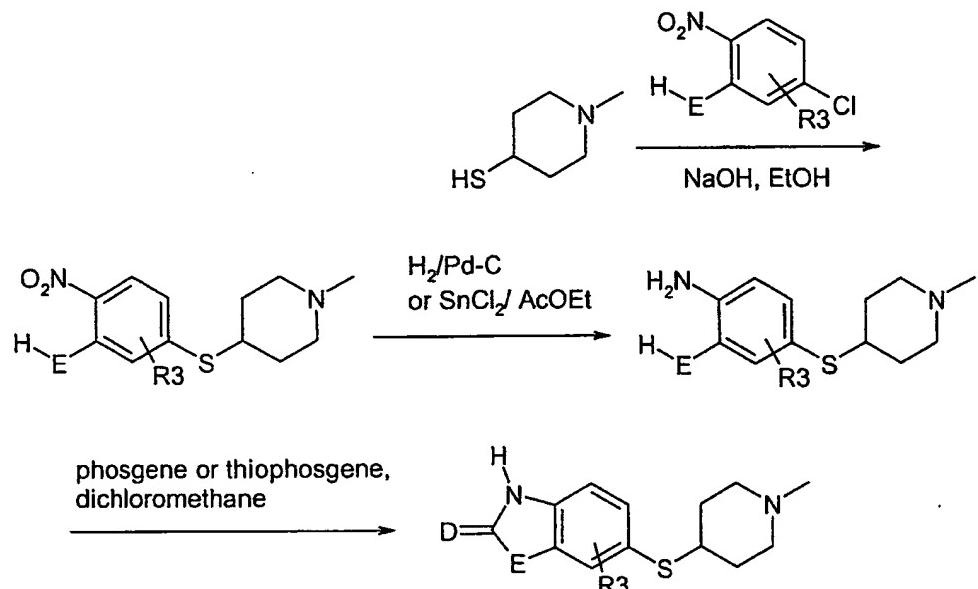


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Substituted compounds of group F¹ and F² (R³ = H, Cl, R⁴ = H, D = O, S and E = O, S, NR⁵, O-CR⁵₂, NR⁵-CR⁵₂, NR⁵-CO) may be prepared by a route exemplified in Scheme 8.

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Reaction Scheme 8

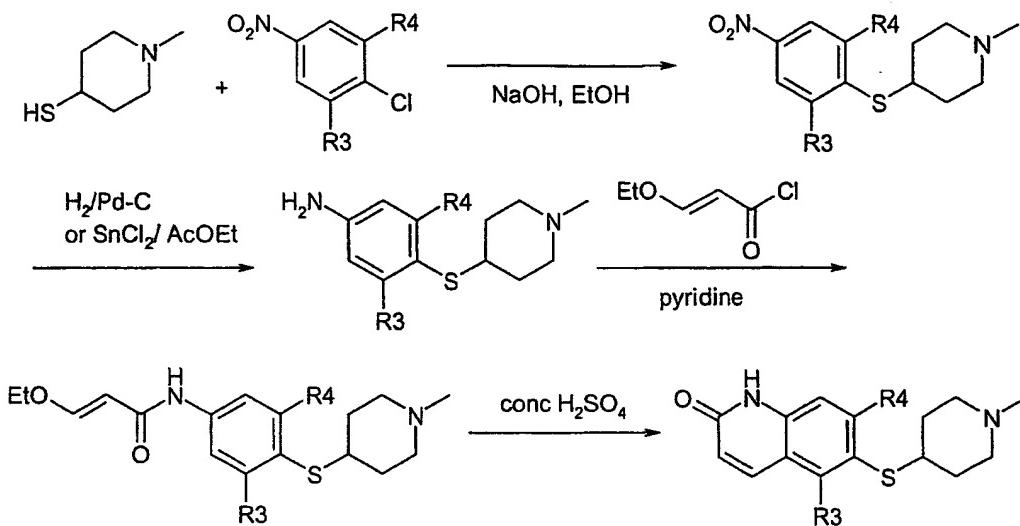
An azamonocyclic thiol (prepared according to *J. Med. Chem.* 1993, 36, 3261) may be used to displace a halo atom (eg chlorine) from an appropriately substituted nitrophenyl derivative in a reaction mediated by a base such as sodium hydride at ambient

- 5 temperature. The resultant nitro derivative may be reduced by catalytic hydrogenation in a protic solvent such as ethanol or by tin chloride in ethyl acetate at reflux temperature. Finally reaction with phosgene (or a synthetic equivalent eg triphosgene) or thiophosgene in a solvent such as dichloromethane or chloroform at a temperature between ambient and reflux temperature gives rise to the compounds of group F¹ and F² specified.

10

Compounds of Group F² where D = O, E = CR⁵=CR⁵ and R3 = R4 may be prepared by a procedure exemplified in Reaction Scheme 9.

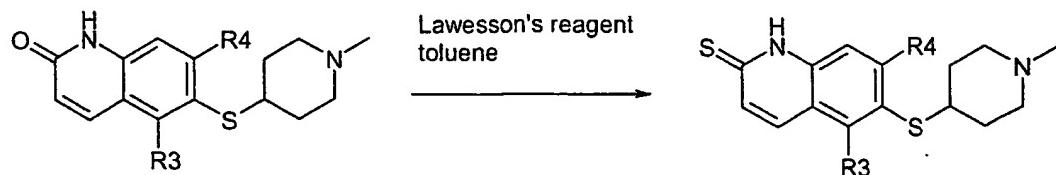
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Reaction Scheme 9

- A thio compound may be used to displace a halo atom (eg chlorine) from an appropriately substituted nitrophenyl derivative in a reaction mediated by a base such as sodium hydride at ambient temperature. The resultant nitro derivative may be reduced by catalytic hydrogenation in a protic solvent such as ethanol or by tin chloride in ethyl acetate at reflux temperature. The aniline derivative so obtained is acylated with (E)-3-ethoxy-2-propenoyl chloride in a solvent such as dichloromethane in the presence of a non-nucleophilic base such as pyridine at a temperature between 0 °C and ambient temperature. The resultant amide may be cyclized with a concentrated mineral acid such as sulphuric acid at a temperature between 0 °C and ambient temperature.
- 5 at ambient temperature. The resultant nitro derivative may be reduced by catalytic hydrogenation in a protic solvent such as ethanol or by tin chloride in ethyl acetate at reflux temperature. The aniline derivative so obtained is acylated with (E)-3-ethoxy-2-propenoyl chloride in a solvent such as dichloromethane in the presence of a non-nucleophilic base such as pyridine at a temperature between 0 °C and ambient
- 10 temperature. The resultant amide may be cyclized with a concentrated mineral acid such as sulphuric acid at a temperature between 0 °C and ambient temperature.

- The conversion of C=O moieties to C=S may be achieved by reaction with Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide] in a solvent such as toluene at refluxing temperature as shown in Scheme 10.
- 15

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Reaction Scheme 10

- The invention also comprehends derivative compounds ("pro-drugs") which are degraded
- 5 in vivo to yield the species of formula (I). Pro-drugs are usually (but not always) of lower potency at the target receptor than the species to which they are degraded. Pro-drugs are particularly useful when the desired species has chemical or physical properties which make its administration difficult or inefficient. For example, the desired species may be only poorly soluble, it may be poorly transported across the mucosal epithelium, or it may
- 10 have an undesirably short plasma half-life. Further discussion of pro-drugs may be found in Stella, V. J. et al., "Prodrugs", *Drug Delivery Systems*, 1985, pp. 112-176, and *Drugs*, 1985, 29, pp. 455-473.

15 Pharmaceutically acceptable salts of the acidic or basic compounds of the invention can of course be made by conventional procedures, such as by reacting the free base or acid with at least a stoichiometric amount of the desired salt-forming acid or base.

20 Pharmaceutically acceptable salts of the acidic compounds of the invention include salts with inorganic cations such as sodium, potassium, calcium, magnesium, and zinc, and salts with organic bases. Suitable organic bases include N-methyl-D-glucamine, arginine, benzathine, diolamine, olamine, procaine and tromethamine.

25 Pharmaceutically acceptable salts of the basic compounds of the invention include salts derived from organic or inorganic acids. Suitable anions include acetate, adipate, besylate, bromide, camsylate, chloride, citrate, edisylate, estolate, fumarate, gluceptate, gluconate, glucuronate, hippurate, hyalate, hydrobromide, hydrochloride, iodide, isethionate, lactate, lactobionate, maleate, mesylate, methylbromide, methylsulfate,

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napsylate, nitrate, oleate, pamoate, phosphate, polygalacturonate, stearate, succinate, sulfate, sulfosalicylate, tannate, tartrate, terephthalate, tosylate and triethyl iodide.

Another aspect of the present invention is a pharmaceutical composition comprising a
5 compound of formula (I) for use in therapy substantially as described hereinbefore with a pharmaceutically acceptable diluent or carrier.

It is anticipated that the compounds of the invention can be administered by oral or parenteral routes, including intravenous, intramuscular, intraperitoneal, subcutaneous,
10 rectal and topical administration, and inhalation.

For oral administration, the compounds of the invention will generally be provided in the form of tablets or capsules or as an aqueous solution or suspension.

15 Tablets for oral use may include the active ingredient mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate and lactose. Corn starch and alginic acid are suitable disintegrating
20 agents. Binding agents may include starch and gelatine. The lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glycetyl monostearate or glycetyl distearate, to delay absorption in the gastrointestinal tract.

25 Capsules for oral use include hard gelatine capsules in which the active ingredient is mixed with a solid diluent and soft gelatine capsules wherein the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

For intramuscular, intraperitoneal, subcutaneous and intravenous use, the compounds of
30 the invention will generally be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Aqueous suspensions according to the invention

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may include suspending agents such as cellulose derivatives, sodium alginate, polyvinyl-pyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate.

- 5 Compounds of the invention have been demonstrated to be active at the neuronal nicotinic beta 4 receptor. Their functional agonist activity has been demonstrated in the test described below.

Functional Ca-flux Assay

10

HEK 293 cell lines expressing different nicotinic receptor $\beta 4$ subtypes are plated at a density of 50,000 cells/well into poly-D-lysine coated 96 well microtitre plates. Twenty-four hours later the cells are washed with buffer and loaded with Fluo-3 dye (10 M) at room temperature for 1h. The dye is removed and 180 μ l of buffer containing atropine at 15 3 μ M added.

The plates are loaded into a FLIPR (Molecular Devices) and 20 μ l of experimental compound are added in a concentration gradient across the plate. The stimulation of the nicotinic receptor response to compound addition is measured as a rise in fluorescence 20 which correlates to the entry of calcium into the cell. Acetylcholine is added 10 min later to all wells to investigate whether the compounds can block the acetylcholine stimulated nicotine response.

25 The effects of compounds as nicotinic agonists and antagonists are calculated using an OMM (Oxford matrix management) curve fit package.

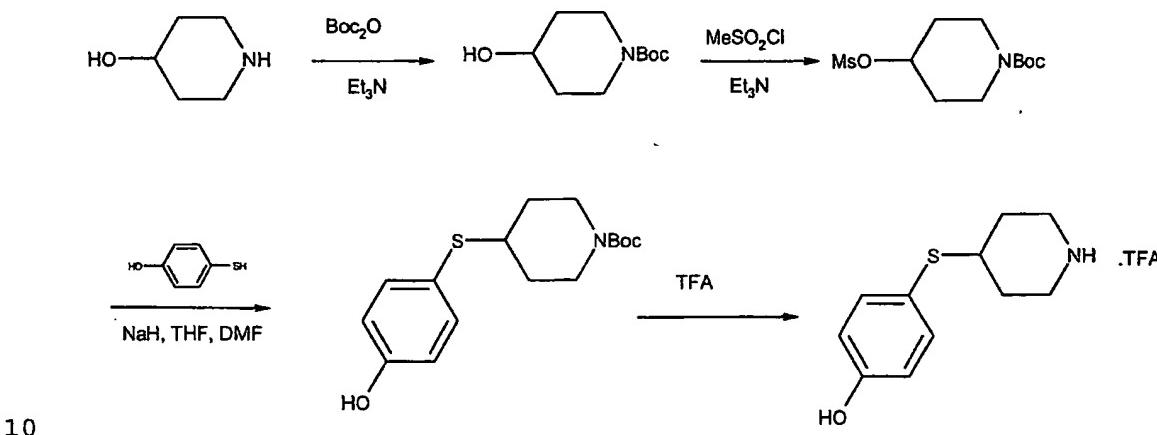
The present invention further provides the use of compounds of formula (I) in the manufacture of a medicament for the treatment of conditions indicating treatment with a 30 beta 4 selective nicotinic acetylcholine receptor modulator and in the manufacture of a medicament for the treatment of dysfunctions of the central and autonomic nervous systems. Such dysfunctions included, for example, dementia, cognitive disorders,

neurodegenerative disorders, extrapyramidal disorders, convulsive disorders, cardiovascular disorders, endocrine disorders, eating disorders, affective disorders, and drug abuse.

- 5 The present invention is now further illustrated by means of the following Examples.

Example 1

4-(4-Hydroxyphenylthio)-piperidine trifluoroacetate



i) 1-(*tert*-Butoxycarbonyl)-4-hydroxy-piperidine

- A mixture of 4-hydroxy-piperidine (10.1 g), triethylamine (14 ml), di-*tert*-butyl dicarbonate (22 g) in dichloromethane (150 ml) is stirred at ambient temperature for 18 hours. The reaction mixture is washed with 150 ml portions of 1.0M hydrochloric acid and water. The organic layer is dried over magnesium sulphate and concentrated to dryness to give the title compound as a colourless oil (20 g). ¹H NMR (300 MHz) (CDCl₃) 3.85 (m, 3H), 3.02 (m, 2H), 1.80 (brm, 3H), 1.50 (brm, 2H), 1.45 (s, 9H).
- 15

20

ii) 1-(*tert*-Butoxycarbonyl)-4-methanesulfonyloxy-piperidine

A mixture of N-(*tert*-butoxycarbonyl)-4-hydroxy-piperidine (6.0g, Reference Example 1), triethylamine (12.5 ml) and dichloromethane (150 ml) is treated dropwise with

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methanesulfonylchloride (3.0 ml) and stirred for 3 hours at ambient temperature. The reaction mixture is washed with 1.0M hydrochloric acid and dried over magnesium sulphate before being concentrated to dryness. The title compound is obtained as a colourless waxy solid. ^1H NMR (300 MHz) (CDCl_3) 4.87 (m, 1H) 3.80 (m, 2H), 3.28 (m, 5 H), 3.01 (s, 3H), 1.95 (m, 2H), 1.80 (m, 2H), 1.45 (s, 9H).

iii) 1-(*tert*-Butoxycarbonyl)-4-(4-hydroxyphenylthio)-piperidine

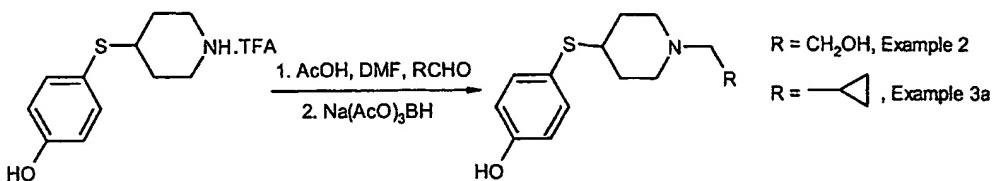
A mixture of 4-mercaptophenol (1.26 g), sodium hydride (0.88g of 60% dispersion in mineral oil), dry tetrahydrofuran (50 ml) and dry dimethylformamide (25 ml) is stirred at ambient temperature for 15 minutes. The resultant reaction mixture is treated with N-(*tert*-butoxycarbonyl)-4-methanesulfonyloxy-piperidine (2.8 g, Reference Example 2) and heated to 70 °C for 6 hours. The reaction mixture is cooled, concentrated to dryness and the residue partitioned between water (100 mL) and dichloromethane (3 x 50 ml). The combined organics were dried over magnesium sulphate and concentrated to leave the title compound as a pale yellow oil (2.2 g). MS (FIA) 332 (100%, M+Na), ^1H NMR (300 MHz) (CDCl_3) 8.01 (s, 1H), 7.20 (m, 2H), 6.90 (m, 2H), 3.98 (m, 1H) 2.95 (m, 5H), 1.86 (m, 2H), 1.45 (m, 1H), 1.44 (s, 9H).

iv) 4-(4-Hydroxyphenylthio)-piperidine trifluoroacetate

A mixture of 1-(*tert*-butoxycarbonyl)-4-(4-hydroxyphenylthio)-piperidine (2.2 g, Reference Example 3), dichloromethane (50 ml) and trifluoroacetic acid (5 ml) is stirred at 0 °C for 3 hours before being concentrated to dryness. The residue is triturated with ether to give the title compound as a colourless amorphous solid (1.0 g). MS (FIA) 242 (100%, M+H), ^1H NMR (300 MHz) (DMSO) 9.85 (br s, 1H), 8.60 (br s, 1H), 7.30 (m, 2H), 6.72 (m, 2H), 3.22 (m, 2H) 3.18 (m, 1H), 2.90 (m, 2H), 1.93 (m, 2H), 1.45 (m, 2H).

Example 2

1-(2-Hydroxyethyl)-4-(4-hydroxyphenylthio)-piperidine



4-(4-hydroxyphenylthio)-piperidine trifluoroacetate (170 mg, Example 1) is dissolved in a mixture of dichloromethane (8 ml) and methanol (4 ml). This solution is treated with MP-carbonate resin (250 mg, Argonaut) and stirred for 1 hour at ambient temperature. The supernatant solution is removed and concentrated to dryness. The residue is dissolved in 1% acetic acid in dimethylformamide (10 ml), treated with glycolaldehyde (65 mg) and allowed to stand at ambient temperature for 2 hours. The resultant reaction mixture is treated with sodium triacetoxyborohydride (200 mg) and allowed to stand at ambient temperature for 18 hours. The solvent is removed in vacuo and the residue partitioned between chloroform (20 ml) and 5% aqueous sodium bicarbonate solution (20 ml). The organic layer is dried over magnesium sulphate and concentrated to dryness. The residue is chromatographed on silica gel eluting with a mixture of dichloromethane and methanol (4/1) to give the title compound as a colourless amorphous solid (50 mg). MS (FIA) 254 (100%, M+H), ^1H NMR (300 MHz) (DMSO) 9.70 (s, 1H), 7.28 (m, 2H), 6.70 (m, 2H), 10 4.30 (m, 1H), 4.05 (br s, 1H), 3.42 (m, 2H), 3.38 (m, 2H), 2.80 (br m, 2H), 2.00 (br m, 2H), 1.78 (br m, 2H), 1.44 (br m, 2H).

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10
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Example 3

(a) 1-(4-Cyclopropylmethyl)-4-(4-hydroxyphenylthio)-piperidine

20 A mixture of 4-(4-hydroxyphenylthio)-piperidine trifluoroacetate (480 mg, Example 1) and MP-carbonate resin (600 mg, Argonaut) in dry dimethylformamide (12ml) is stirred for 1 hour at ambient temperature. The supernatant solution is removed and a 0.5 ml aliquot was added to a solution of cyclopropanecarboxaldehyde (9 mg) in 1% acetic acid/dimethylformamide (0.5 ml). This reaction mixture is allowed to stand at ambient temperature for 2 hours before being treated with 0.5 ml of a 0.25M solution of sodium triacetoxyborohydride (200 mg) in 1% acetic acid/dimethylformamide. The reaction mixture is allowed to stand at ambient temperature for a further 18 hours. The solvent is removed in vacuo and the residue partitioned between chloroform (2 ml) and 5% aqueous

25

- sodium bicarbonate solution (1 ml). The organic layer is separated and concentrated to dryness. The residue is dissolved in methanol (2 ml) and applied to a 3 ml SCX ion exchange column (Jones Chromatography, preconditioned with 2 x 2ml methanol). The column was eluted with methanol (2 x 2ml) and 2.0M ammonia in methanol (2 x 2ml).
- 5 The ammonia/ methanol fractions was concentrated in vacuo to leave the title compound as a yellow oil. LCMS 264 (100%, M+H), Rt = 1.9 min (gradient 95:5 water:acetonitrile to 95:5 acetonitrile:water over 8 min).
- By proceeding in a similar manner but using the appropriate aldehyde in place of cyclopropanecarboxaldehyde there is prepared:
- 10
- (b) (*R/S*)-1-(2,3-Dihydroxy-1-propyl)-4-(4-hydroxyphenylthio)-piperidine
LCMS 284 (100%, M+H), Rt = 1.4 min.
- 15 (c) 1-(Cyclohexylmethyl)-4-(4-hydroxyphenylthio)-piperidine
LCMS 306 (95%, M+H), Rt = 2.6 min.
- 20 (d) 1-(2-Furanyl methyl)-4-(4-hydroxyphenylthio)-piperidine
LCMS 290 (82%, M+H), Rt = 2.1 min.
- (e) 1-(2-Methyl-1-propyl)-4-(4-hydroxyphenylthio)-piperidine
LCMS 266 (100%, M+H), Rt = 2.0 min.
- 25 (f) 1-(4-Methoxybenzyl)-4-(4-hydroxyphenylthio)-piperidine
LCMS 330 (95%, M+H), Rt = 2.4 min.
- (g) 1-Benzyl-4-(4-hydroxyphenylthio)-piperidine
LCMS 300 (100%, M+H), Rt = 2.3 min.
- 30 (h) 1-(n-Butyl)-4-(4-hydroxyphenylthio)-piperidine
LCMS 266 (93%, M+H), Rt = 2.1 min.

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(i) 1-(3-Methyl-1-butyl)-4-(4-hydroxyphenylthio)-piperidine

LCMS 280 (92%, M+H), Rt = 2.4 min.

(j) 1-(2-Hydroxyethyl)-4-(4-hydroxyphenylthio)-piperidine

5 LCMS 254 (93%, M+H), Rt = 1.4 min.

(k) 1-(2-Imidazolylmethyl)-4-(4-hydroxyphenylthio)-piperidine

LCMS 290 (100%, M+H), Rt = 1.6 min.

10 **(l) 1-(1-Methyl-2-pyrrolylmethyl)-4-(4-hydroxyphenylthio)-piperidine**

LCMS 303 (74%, M+H), Rt = 2.2 min.

(m) 1-(2-phenethyl)-4-(4-hydroxyphenylthio)-piperidine

LCMS 314 (35%, M+H), Rt = 2.6 min.

15

(n) 1-(n-Propyl)-4-(4-hydroxyphenylthio)-piperidine

LCMS 252 (90%, M+H), Rt = 1.8 min.

(o) 1-(2-Pyridylmethyl)-4-(4-hydroxyphenylthio)-piperidine

20 LCMS 301 (100%, M+H), Rt = 1.9 min.

(p) 1-(2-Thiophenylmethyl)-4-(4-hydroxyphenylthio)-piperidine

LCMS 306 (97%, M+H), Rt = 2.2 min.

25

(q) 1-(2,2-Dimethyl-1-propyl)-4-(4-hydroxyphenylthio)-piperidine

LCMS 280 (84%, M+H), Rt = 1.5 min.

(r) 1-(2-Phenyl-4-imidazolylmethyl)-4-(4-hydroxyphenylthio)-piperidine

LCMS 366 (72%, M+H), Rt = 2.3 min.

30

(s) 1-(1-Oxo-4-pyridylmethyl)-4-(4-hydroxyphenylthio)-piperidine

LCMS 317 (100%, M+H), Rt = 1.4 min.

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(t) 1-(1-Methyl-2-imidazolylmethyl)-4-(4-hydroxyphenylthio)-piperidine

LCMS 304 (100%, M+H), Rt = 1.9 min.

5 **(u) 1-(2-Thiazolylmethyl)-4-(4-hydroxyphenylthio)-piperidine**

LCMS 307 (100%, M+H), Rt = 1.9 min.

(v) 1-(3,3-Dimethyl-1-butyl)-4-(4-hydroxyphenylthio)-piperidine

LCMS 294 (100%, M+H), Rt = 2.6 min.

10

(w) (R/S)-1-(2-Methyl-1-butyl)-4-(4-hydroxyphenylthio)-piperidine

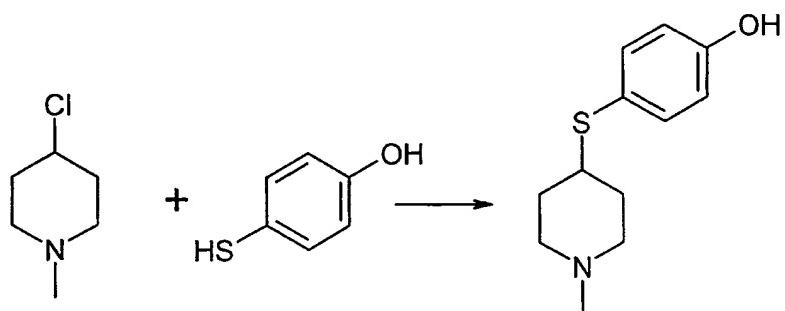
LCMS 280 (100%, M+H), Rt = 2.3 min.

(x) 1-(3-Methylthio-1-propyl)-4-(4-hydroxyphenylthio)-piperidine

15 LCMS 298 (69%, M+H), Rt = 2.1 min.

Example 4

4-(1-methylpiperidin-4-yl)thiophenol



20

4-chloro-1-methylpiperidine (5.0 g, 29.4 mmol) 4-hydroxythiophenol (3.7 g, 29.4 mmol),

K₂CO₃ (12.0 g, 88.2 mmol) and anhydrous DMF (90 mL) afforded 2.85 g (43%) of the

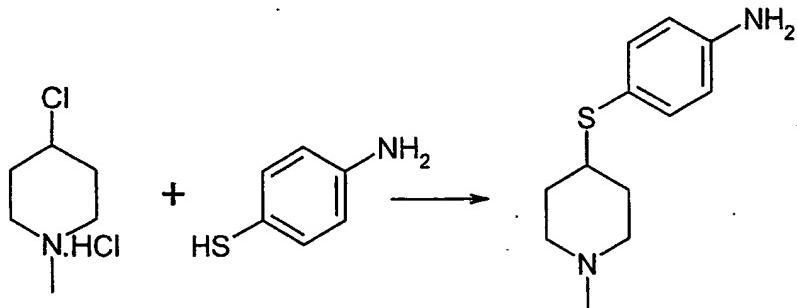
desired compound which is converted to the hydrochloride salt. ¹H NMR (CDCl₃) 7.23
(m, 2H), 6.64 (m, 2H), 3.38-3.18 (m, 3H), 2.92-2.69 (m, 2H), 2.69 (s, 3H), 2.05-2.00 (m,

25 2H), 1.62-1.57 (m, 2H); mp 170-172°C; LRMS (EI) m/e 223.

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Example 5

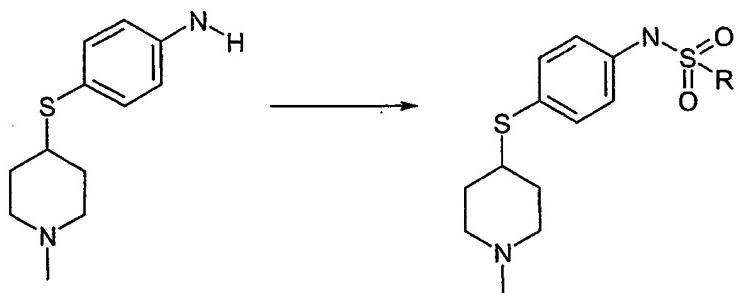
4-(1-methylpiperidin-4-yl)thiophenylamine



- 4-chloro-1-methylpiperidine hydrochloride (6.46 g, 38 mmol) 4-mercaptopaniline (5.0 g,
 5 40.0 mmol), K₂CO₃ (16.5 g, 120 mmol) and anhydrous DMF (120 mL) afforded 1.9 g
 (21%) of the desired compound which is converted to the hydrochloride salt. ¹H NMR
 (CDCl₃) 7.19 (m, 2H), 6.52 (m, 2H), 3.69 (brs, 2H 2.74-2.70 (m, 3H), 2.15 (s, 3H), 1.92-
 1.79 (m, 4H), 1.59-1.47 (m, 2H); mp 96-98°C; LCMS m/z 222 (M⁺).

10 Example 6

(a) N-{4-[1-methylpiperidin-4-yl]thio}phenyl}-2-chlorophenylsulphonamide



- In a typical procedure, 4-(1-methylpiperidin-4-yl)thiophenylamine is stirred for 12 hours
 with 1 equivalent of 2-chlorophenylsulphonyl chloride and 1 equivalent of pyridine in
 15 dichloromethane. The solvents are removed in vacuo and the residue purified by
 preparative HPLC to give an oil, LCMS 397 (100%, M+H).

By proceeding in a similar manner, using the appropriate arylsulphonyl chloride there
 were prepared the following examples:

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(b) N-{4-[(1-methylpiperidin-4-yl)thio]phenyl}-2-nitrophenylsulphonamide
LCMS 408 (100%, M+H).

(c) N-{4-[(1-methylpiperidin-4-yl)thio]phenyl}-4-bromophenylsulphonamide
5 LCMS 442 (100%, M+H).

(d) N-{4-[(1-methylpiperidin-4-yl)thio]phenyl}-2-nitro-4-trifluoromethylphenylsulphonamide
LCMS 476 (100%, M+H).

10 (e) N-{4-[(1-methylpiperidin-4-yl)thio]phenyl}-2-chloro-3-nitrophenylsulphonamide
LCMS 442 (100%, M+H).

15 (f) N-{4-[(1-methylpiperidin-4-yl)thio]phenyl}-4-methoxyphenylsulphonamide
LCMS 393 (100%, M+H).

(g) N-{4-[(1-methylpiperidin-4-yl)thio]phenyl}-4-fluorophenylsulphonamide
LCMS 381 (100%, M+H).

20 (h) N-{4-[(1-methylpiperidin-4-yl)thio]phenyl}-4-methylphenylsulphonamide
LCMS 377 (100%, M+H).

25 (i) N-{4-[(1-methylpiperidin-4-yl)thio]phenyl}-4-methoxy-2-nitrophenylsulphonamide
LCMS 438 (100%, M+H).

(j) N-{4-[(1-methylpiperidin-4-yl)thio]phenyl}-2-naphthylsulphonamide
LCMS 413 (100%, M+H).

30 (k) N-{4-[(1-methylpiperidin-4-yl)thio]phenyl}-2,4,6-trimethylphenylsulphonamide

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LCMS 405 (100%, M+H).

(l) N-{4-[(1-methylpiperidin-4-yl)thio]phenyl}-4-methyl-2-methoxyphenylsulphonamide

5 LCMS 407 (100%, M+H).

(m) N-{4-[(1-methylpiperidin-4-yl)thio]phenyl}-4-chlorophenylsulphonamide

LCMS 397 (100%, M+H).

10 (n) N-{4-[(1-methylpiperidin-4-yl)thio]phenyl}-2,5-dichloro-3-thiophenylsulphonamide

LCMS 438 (100%, M+H).

(o) N-{4-[(1-methylpiperidin-4-yl)thio]phenyl}-4-isopropylphenylsulphonamide

15 LCMS 405 (100%, M+H).

(p) N-{4-[(1-methylpiperidin-4-yl)thio]phenyl}-4-ethylphenylsulphonamide

LCMS 391 (100%, M+H).

20 (q) N-{4-[(1-methylpiperidin-4-yl)thio]phenyl}-4-methoxy-2,5,6-trimethylphenylsulphonamide

LCMS 435 (100%, M+H).

(r) N-{4-[(1-methylpiperidin-4-yl)thio]phenyl}-3-methoxyphenylsulphonamide

25 LCMS 493 (100%, M+H).

(s) N-{4-[(1-methylpiperidin-4-yl)thio]phenyl}-4-methanesulphonylphenylsulphonamide

LCMS 441 (100%, M+H).

30

(t) N-{4-[(1-methylpiperidin-4-yl)thio]phenyl}-2,5-dimethylphenylsulphonamide

LCMS 390 (100%, M+H).

(u) N-{4-[(1-methylpiperidin-4-yl)thio]phenyl}-2,3,4-trifluorophenylsulphonamide

LCMS 417 (100%, M+H).

5

(v) N-{4-[(1-methylpiperidin-4-yl)thio]phenyl}-4-acetylaminophenylsulphonamide

LCMS 420 (100%, M+H).

10 (w) N-{4-[(1-methylpiperidin-4-yl)thio]phenyl}-4-trifluoromethoxyphenylsulphonamide

LCMS 448 (100%, M+H).

15 (x) N-{4-[(1-methylpiperidin-4-yl)thio]phenyl}-3-bromophenylsulphonamide
LCMS 442 (100%, M+H).

(y) N-{4-[(1-methylpiperidin-4-yl)thio]phenyl}-3,4-dichlorophenylsulphonamide
LCMS 432 (100%, M+H).

20 (z) N-{4-[(1-methylpiperidin-4-yl)thio]phenyl}-3-cyanophenylsulphonamide
LCMS 388 (100%, M+H).

25 (aa) N-{4-[(1-methylpiperidin-4-yl)thio]phenyl}-2-trifluoromethoxyphenylsulphonamide
LCMS 447 (100%, M+H).

(ab) N-{4-[(1-methylpiperidin-4-yl)thio]phenyl}-3-methoxycarbonyl-2-thiophenylsulphonamide
LCMS 427 (100%, M+H).

30

(ac) N-{4-[(1-methylpiperidin-4-yl)thio]phenyl}-4-n-hexylphenylsulphonamide
LCMS 433 (100%, M+H).

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(ad) N-{4-[(1-methylpiperidin-4-yl)thio]phenyl}-4-bromo-2-

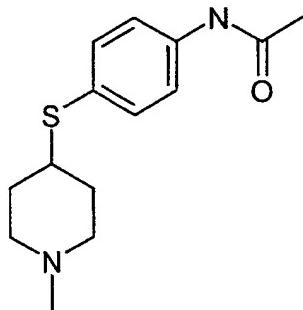
methylphenylsulphonamide

LCMS 456 (100%, M+H).

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Example 7

N-{4-[(1-methylpiperidin-4-yl)thio]phenyl}acetamide



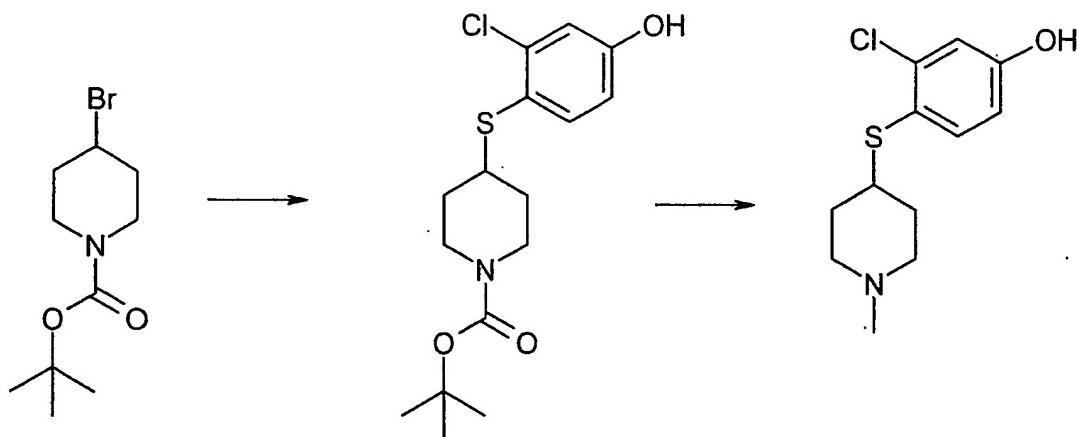
4-methanesulfonate-1-methylpiperidine hydrochloride (1.58 g, 8.19 mmol) 4-acetamido-thiophenol (1.52 g, 8.19 mmol), K₂CO₃ (5.66 g, 4.97 mmol) and anhydrous DMF (30 mL) afforded 350 mg (14%) of the desired compound which is converted to the fumaric salt. ¹H NMR (CDCl₃) 7.57 (m, 2H), 7.44 (m, 2H), 6.68 (s, 2H), 3.4 (m, 2H), 3.3 (m, 1H), 3.05 (m, 2H), 2.15 (m, 2H) 2.11 (s, 3H), 2.11 (m, 2H), mp 199-201°C; LCMS m/z 265 (MH⁺).

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Example 8

3-Chloro-4-(1-methylpiperidin-4-yl)thiophenol

-55-

i) ***Tert*-butyl-4-bromopiperidine-1-carboxylate**

- 5 Prepared in 88% yield following the procedure described for *tert*-butyl-(3*R*)-3-hydroxy pyrrolidine-1-carboxylate using *tert*-butyl-4-hydroxypiperidine-1-carboxylate (1 g, 4.95 mmol), carbon tetrabromide (2.46 g, 7.42 mmol), and triphenylphosphine (1.95 g, 7.42 mmol) in CH₂Cl₂ (25 mL). ¹H NMR (CDCl₃) 4.37-4.32 (m, 1H), 3.72-3.64 (m, 2H), 3.35-3.27 (m, 2H), 2.12-2.04 (m, 2H), 1.98-1.88 (m, 2H), 1.46 (s, 9H).

10

ii) ***Tert*-butyl-4-[2-chloro-4-hydroxyphenyl]thio)piperidine-1-carboxylate**

- Prepared in 70% yield following the procedure described for *tert*-butyl-(3*R*)-3-[(2-chloro-4-hydroxyphenyl)thio]pyrrolidine-1-carboxylate using *tert*-butyl-4-bromo piperidine-1-carboxylate (200 mg, 0.76 mmol), 2-chloro-4-hydroxythiophenol (134 mg, 0.84 mmol), and K₂CO₃ (315 mg, 2.28 mmol) in DMF (8 mL) as starting mixture. ¹H NMR (CDCl₃) 7.64 (s, 1H), 7.38 (d, J = 8.43 Hz, 1H), 7.00 (s, 1H), 6.72 (dd, J = 8.43, 2.52 Hz, 1H), 3.95 (m, 2H), 3.19 (m, 1H), 2.93 (bs, 2H), 1.82 (bs, 2H), 1.52 (m, 2H), 1.46 (s, 9H).

20 iii) **3-Chloro-4-(1-methylpiperidin-4-yl)thiophenol**

Prepared following the procedure described for 3-chloro-4-[(3*R*)-1-methylpyrrolidin-3-yl]thiophenol in 59% yield using *tert*-butyl-4-[(2-chloro-4-hydroxyphenyl)thio]piperidine-1-carboxylate (180 mg, 0.52 mmol) and AlLiH₄ (1M in THF, 1.2 mL, 1.14

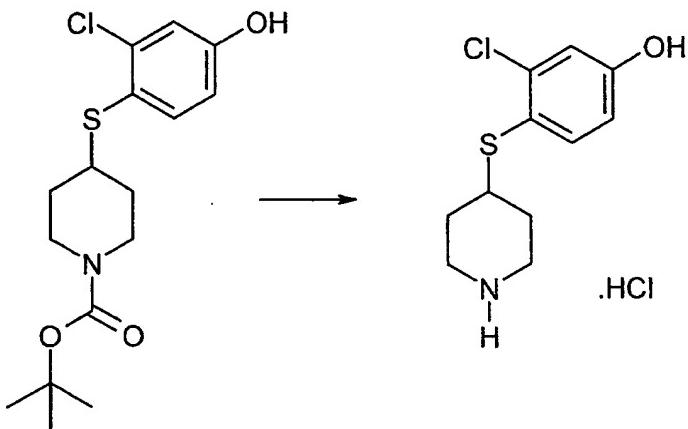
-56-

mmol) in CH₂Cl₂ (5.2 mL) as starting mixture followed by subsequent addition of 0.5 mL of AlLiH₄. ¹H NMR (CDCl₃) 7.40 (d, J = 8.46 Hz, 1H), 6.90 (s, 1H), 6.68 (dd, J = 8.43, 2.61 Hz, 1H), 3.56 (m, 1H), 3.31-3.29 (m, 2H), 2.29 (s, 3H), 2.18 (m, 2H), 1.93-1.87 (m, 2H), 1.64-1.59 (m, 2H); LCMS m/z 258 (M⁺); Rf = 0.47 (CHCl₃:MeOH, 8:2).

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Example 9

3-Chloro-4-(piperidin-4-yl)thiophenol.hydrochloride

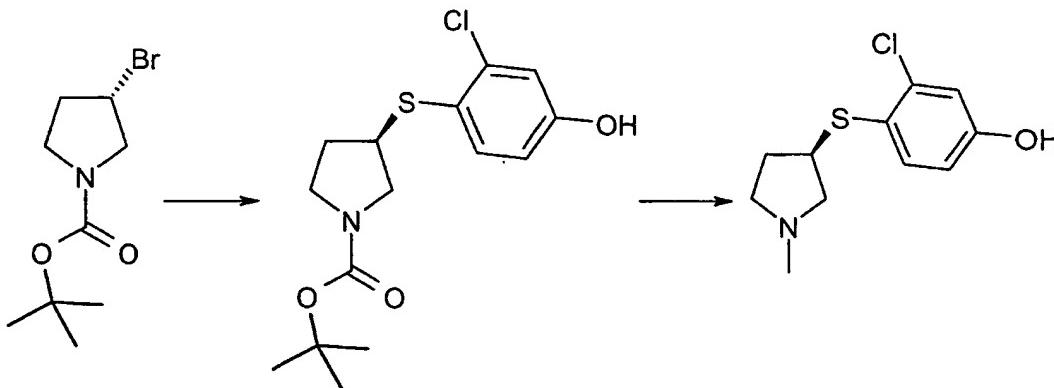


To a solution of *tert*-butyl-4-[(2-chloro-4-hydroxyphenyl)thio]piperidine-1-carboxylate (160 mg, 0.46 mmol) in CH₂Cl₂ (5 mL) is added HCl (4M in 1,4-dioxane, 0.25 mL, 0.92 mmol). The resulting clear solution is stirred at room temperature overnight under Argon. The white precipitate is filtered, washed with ether, and dried to afford 93.4 mg (84%) of the desired compound. ¹H NMR (CD₃OD) 7.46 (d, J = 8.52 Hz, 1H), 6.93 (s, 1H), 6.73 (dd, J = 8.52, 2.61 Hz, 1H), 3.44-3.29 (m, 3H), 3.09-3.00 (m, 2H), 2.15-2.08 (m, 2H), 1.81-1.70 (m, 2H); ¹³C NMR (CD₃OD) 159.1, 139.5, 137.9, 119.6, 116.6, 114.6, 42.7, 41.2, 28.4; LCMS m/z 245 (M⁺+1); Rf = 0.40 (*n*-BuOH:H₂O:AcOH, 6:2:2).

Example 10

3-chloro-4-[(3R)-1-methylpyrrolidin-3-yl]thiophenol

-57-



i) ***Tert*-butyl-(3*S*)-3-bromopyrrolidine-1-carboxylate**

A mixture of *tert*-butyl-(3*R*)-3-hydroxypyrrolidine-1-carboxylate (500 mg, 2.67 mmol) and triphenylphosphine (1 g, 4 mmol) in anhydrous CH₂Cl₂ (10 mL) is cooled to 0-5 °C under Argon. Carbon tetrabromide (1.33 g, 4 mmol) dissolved in CH₂Cl₂ (5 mL) is then slowly added keeping the temperature below 10 °C. The resulting yellow mixture is allowed to warm to room temperature and stirred overnight. The solvent is removed *in vacuo* and the viscous yellow residue is purified by flash chromatography (silica gel, Hexane:EtOAc, 3:1 and then 1:1) to afford 520 g (78%) of the compound as a colorless oil. ¹H NMR (CDCl₃) 4.48 (bs, 1H), 3.82-3.46 (m, 4H), 2.36-2.20 (m, 2H), 1.47 (s, 9H).

ii) ***tert*-butyl-(3*R*)-3-[(2-chloro-4-hydroxyphenyl)thio] pyrrolidine-1-carboxylate**

tert-butyl-(3*S*)-3-bromopyrrolidine-1-carboxylate (400 mg, 1.6 mmol), 2-chloro-4-hydroxythiophenol (308 mg, 1.92 mmol), K₂CO₃ (662 mg, 4.8 mmol) and anhydrous DMF (16 mL) afforded 457 mg (87%) of the desired compound as a white solid. ¹H NMR (CDCl₃) 7.30 (d, *J* = 8.37 Hz, 1H), 6.98 (s, 1H), 6.72 (d, *J* = 7.92 Hz, 1H), 3.72-3.66 (bs, 1H), 3.61-3.48 (m, 2H), 3.43-3.28 (m, 2H), 2.24-2.08 (m, 1H), 1.97-1.81 (m, 1H), 1.48 (s, 1H).

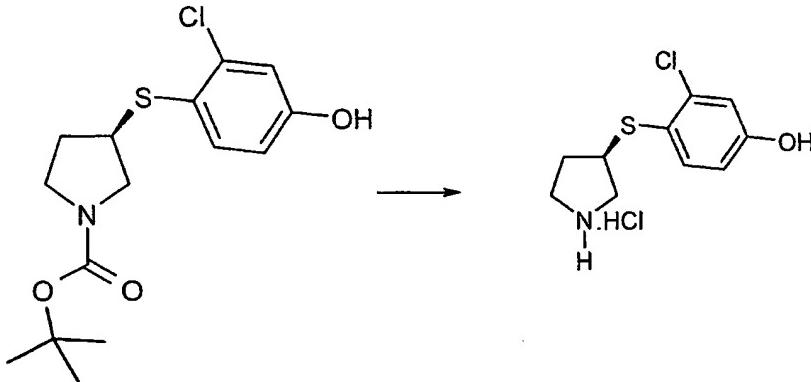
iii) **3-chloro-4-[(3*R*)-1-methylpyrrolidin-3-yl]thiophenol**

To a stirred solution of *tert*-butyl-(3*R*)-3-[(2-chloro-4-hydroxyphenyl)thio] pyrrolidine-1-carboxylate (200 mg, 0.61 mmol) in anhydrous THF (10 mL) under Argon is added

AlLiH₄ (1M in THF, 1.3 mL, 1.34 mmol) at room temperature. The resulting clear solution is stirred at room temperature overnight. 1.7 equivalents of AlLiH₄ (1M in THF, 1 mL, 1 mmol) is added and the stirring is extended for 2 days. H₂O is slowly added to quench the reaction. The white precipitate is filtered and washed with CH₂Cl₂ and EtOAc. The organics are washed with a saturated NaCl solution (2x), combined, dried over Na₂SO₄, and concentrated under reduced pressure to give a yellow oil. Purification by flash chromatography (silica gel, CHCl₃ and then CHCl₃: MeOH, 95:5) afforded 50 mg (34%) of the desired compound as a yellow oil. ¹H NMR (CDCl₃) 7.66 (bs, 1H), 7.28 (d, *J* = 8.37 Hz, 1H), 6.84 (s, 1H), 6.59 (dd, *J* = 8.46, 2.52 Hz, 1H), 3.75-3.70 (m, 1H), 3.08-3.02 (m, 1H), 2.81-2.74 (m, 2H), 2.60-2.54 (m, 1H), 2.44 (s, 3H), 2.33-2.25 (m, 1H), 1.89-1.85 (m, 1H); ¹³C NMR (CDCl₃) 158.6, 138.1, 135.9, 122.2, 117.8, 115.4, 62.0, 55.1, 43.9, 41.9, 31.8; LCMS m/z 244 (M⁺), Rf = 0.53 (CHCl₃:MeOH, 8:2).

Example 11

15 **3-Chloro-4-[(3R)-pyrrolidin-3-yl]thiophenol.hydrochloride**



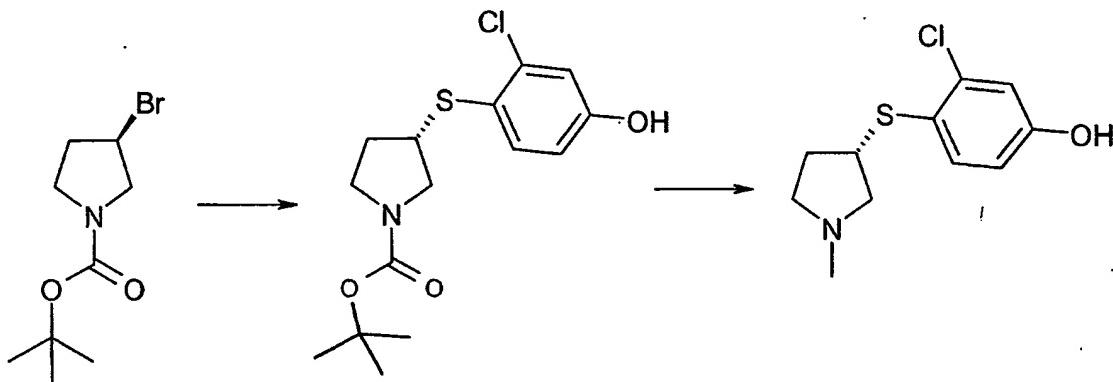
To a stirred solution of *tert*-butyl-(3R)-3-[(2-chloro-4-hydroxyphenyl)thio] pyrrolidine -1-carboxylate (100 mg, 0.3 mmol) in anhydrous CH₂Cl₂ (2 mL) and MeOH (1 mL) under Argon is added HCl (4M in 1,4-dioxane, 0.15 mL). The resulting clear solution is stirred at room temperature overnight. More HCl (4M in 1,4-dioxane, 0.15 mL) is added and the mixture is stirred for 5 hr. The solvent is removed in vacuo and the residue was purified by preparative HPLC (Phenominex Polar-RP, 1" x 10 cm x 4 micron, A: H₂O/TFA, 100:0.1, B: ACN/TFA, 100:0.05, gradient from A to B over 15 min, Rf = 8 min, UV = 254 nm). ¹H NMR (CD₃OD) 7.48 (d, *J* = 8.4 Hz, 1H), 6.95 (s, 1H), 6.75 (dd, *J* = 8.4, 2.4

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Hz, 1H), 3.94 (qt, $J = 6.3$ Hz, 1H), 3.5 (m, 2H), 3.36 (m, 1H), 3.18 (m, 1H), 2.33 (m, 1H), 1.95 (m, 1H); ^{13}C NMR (CD_3OD) 159.8, 139.4, 137.8, 120.1, 117.1, 115.1, 50.4, 44.6, 44.6, 30.4; LCMS m/z 230 ($M^+ + 1$); $R_f = 0.36$ ($n\text{-BuOH:H}_2\text{O:AcOH}$, 6:2:2).

5 Example 12

3-Chloro-4-[(3S)-1-methylpyrrolidin-3-yl]thiophenol



i) **Tert-butyl-(3R)-3-bromopyrrolidine-1-carboxylate**

10 Prepared following the procedure described for *tert*-butyl-(3R)-3-hydroxypyrrolidine-1-carboxylate using *tert*-butyl-(3S)-3-hydroxypyrrolidine-1-carboxylate (500 mg, 2.67 mmol), carbon tetrabromide (1.32 g, 4 mmol), and triphenylphosphine (1 g, 4 mmol) in CH_2Cl_2 (25 mL) as starting mixture. The desired compound is obtained as a clear liquid in 80% yield. ^1H NMR (CDCl_3) 4.48 (bs, 1H), 3.80-3.48 (m, 4H), 2.33-2.24 (m, 2H), 15 1.46 (s, 9H).

ii) **Tert-butyl-(3S)-3-[(2-chloro-4-hydroxyphenyl)thio]pyrrolidine-1-carboxylate**

Prepared following the procedure described for *tert*-butyl-(3R)-3-[(2-chloro-4-hydroxyphenyl)thio]pyrrolidine-1-carboxylate using *tert*-butyl-(3R)-3-bromopyrrolidine-1-carboxylate (480 mg, 1.92 mmol), 2-chloro-4-hydroxythiophenol (338 mg, 2.11 mmol), and K_2CO_3 (795 mg, 5.76 mmol) in DMF (20 mL) as starting mixture. The desired compound is obtained as a white solid in 83% yield. ^1H NMR (CDCl_3) 7.36 (d, $J = 8.37$ Hz, 1H), 7.00 (s, 1H), 6.74 (d, $J = 7.90$ Hz, 1H), 3.72-3.68 (m, 1H), 3.61-3.49 (m, 2H), 3.43-3.33 (m, 2H), 2.19-2.08 (m, 1H), 1.97-1.81 (m, 1H), 1.47 (s, 1H).

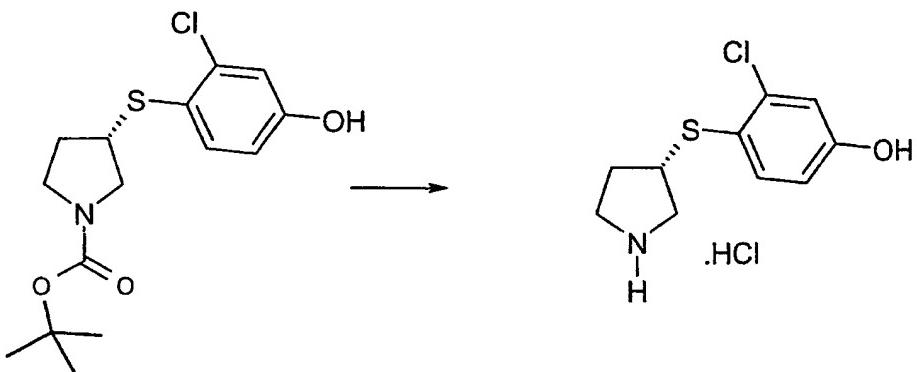
-60-

iii) 3-Chloro-4-[(3S)-1-methylpyrrolidin-3-yl]thiophenol

- Prepared following the procedure described for 3-chloro-4-[(3R)-1-methylpyrrolidin-3-yl]thiophenol using *tert*-butyl-(3S)-3-[(2-chloro-4-hydroxyphenyl)thio]pyrrolidine-1-carboxylate (250 mg, 0.76 mmol) and AlLiH₄ (1M in THF, 1.5 mL, 1.52 mmol) in THF (8 mL) followed by subsequent addition of 1 mL of AlLiH₄. The desired compound is obtained as a white foam in 35% yield. ¹H NMR (CDCl₃) 7.84 (bs, 1H), 7.27 (d, *J* = 8.28 Hz, 1H), 6.83 (s, 1H), 6.59 (dd, *J* = 8.46, 2.58 Hz, 1H); 3.75-3.70 (m, 1H), 3.09-3.04 (m, 1H), 2.82-2.74 (m, 2H), 2.60-2.55 (m, 1H), 2.44 (s, 3H), 2.31-2.26 (m, 1H), 1.89-1.85 (m, 1H); ¹³C NMR (CDCl₃) 158.6, 138.1, 135.9, 122.1, 117.8, 115.4, 61.9, 55.1, 43.9, 41.9, 31.7; LCMS m/z 244 (M⁺); Rf = 0.59 (CHCl₃:MeOH, 8:2).

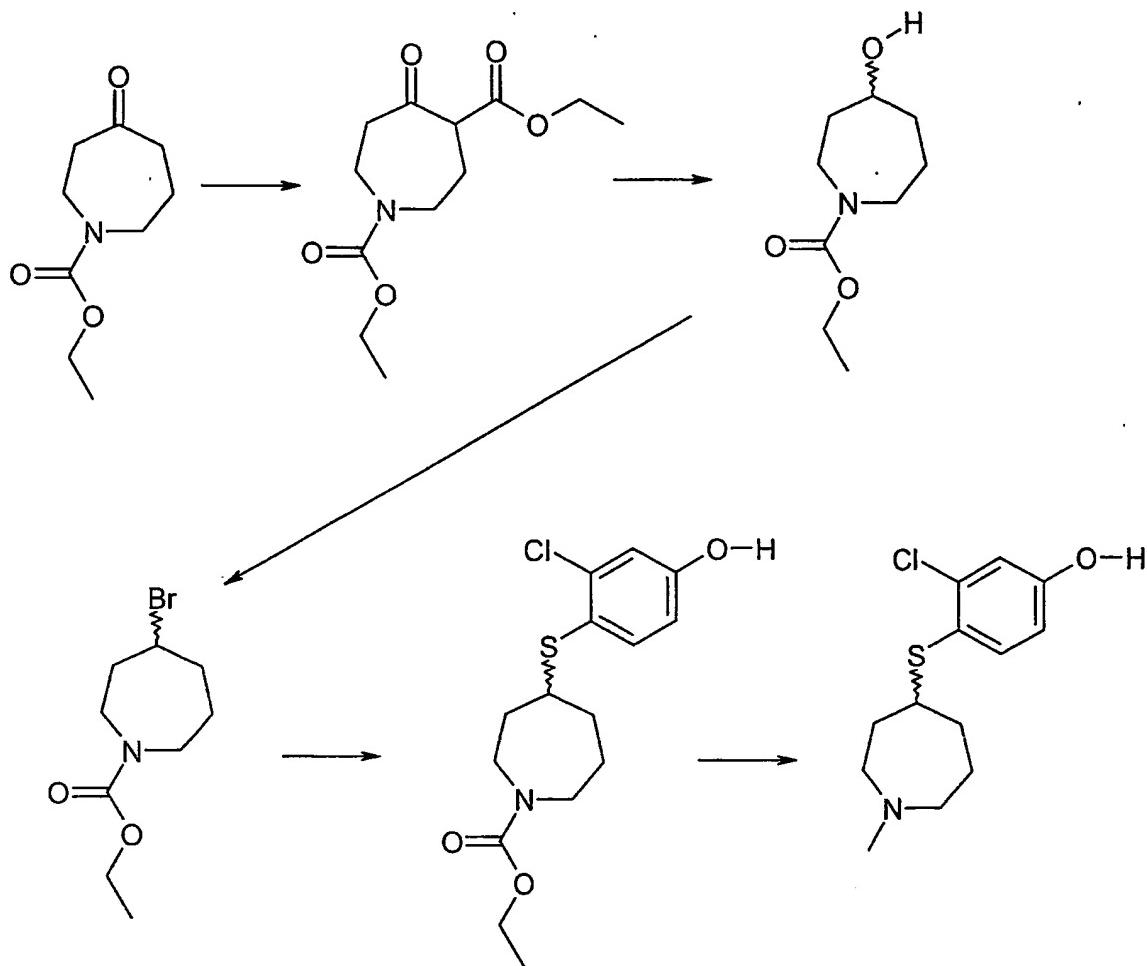
Example 13

3-Chloro-4-[(3S)-pyrrolidin-3-yl]thiophenol.hydrochloride



15

- Prepared following the procedure described for 3-Chloro-4-[(3R)-pyrrolidin-3-yl]thiophenol.hydrochloride using *tert*-butyl-(3S)-3-[(2-chloro-4-hydroxyphenyl)thio]pyrrolidine-1-carboxylate (100 mg, 0.3 mmol) and HCl (4M in dioxane, 0.15 mL, 0.6 mmol) in CH₂Cl₂ (5 mL). The solvent is removed in vacuo and the residue is purified by preparative HPLC (Phenominex Polar-RP, 1" x 10 cm x 4 micron, A: H₂O/TFA, 100:0.1, B: ACN/TFA, 100:0.05, gradient from A to B over 15 min, Rf = 8 min, UV = 254 nm). ¹H NMR (CD₃OD) 7.47 (d, *J* = 8.55 Hz, 1H), 6.95 (s, 1H), 6.75 (dd, *J* = 8.46, 2.61 Hz, 1H), 3.94 (m, 1H), 3.5 (m, 2H), 3.48 (m, 1H), 3.18 (m, 1H), 2.33 (m, 1H), 1.95 (m, 1H); ¹³C NMR (CD₃OD) 161.4, 140.9, 139.3, 122.0, 118.6, 116.6, 51.9, 46.1, 46.0, 31.9; LCMS m/z 230 (M⁺+1); Rf = 0.33 (*n*-BuOH:H₂O:AcOH, 6:2:2).

Example 14**3-Chloro-4-[(1-methylazepan-4-yl)thio]phenol**

5

i) **Diethyl-5-oxoazepane-1,4-dicarboxylate**

Solutions of boron trifluoride etherate (7.4 ml, 58.4 mmol) and ethyl diazoacetate (8.1 ml) each in anhydrous diethyl ether (6.2 ml) are added simultaneously over 45 minutes to a stirred solution of 1-carbethoxypiperidine-4-one (8.8 ml, 58.4 mmol) and anhydrous diethyl ether (20 ml), maintaining temperature between -25°C to -33°C under argon. After addition is completed, let mixture stir for an additional hour at -30°C and then allow to warm to room temperature. Carefully add 30% potassium carbonate (100 ml) and extract mixture with ethyl acetate (3 x 20 ml). Combined organic extracts are dried over magnesium sulfate, filtered and concentrated *in vacuo* to give a yellow oil (15.0 g, 100%).

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¹H NMR (300 MHz, CDCl₃): 4.26-4.08 (m, 4H), 3.9-3.73 (m, 3H), 3.52-3.4 (2H), 2.84-2.7 (m, 2H), 2.08-2.04 (m, 2H), 1.37-1.22 (m, 6H).

ii) **Ethyl-4-oxoazepane-1-carboxylate**

- 5 Diethyl-5-oxoazepane-1,4-dicarboxylate (15.0 g, 58.3 mmol) is refluxed in 4N HCl (220 ml) for six hours under argon. Mixture is allowed to cool to room temperature and stirred overnight. Reaction mixture is concentrated *in vacuo* to afford a red oil. Added water (45 ml) and cooled to -5°C in methanol / ice bath. Added portions of 30% potassium carbonate aqueous solution until pH 11 and then over 20 minutes added ethyl
10 chloroformate maintaining temperature between -7°C to -2°C. Let mixture stir for two hours at 0°C and allow to warm to room temperature overnight. Reaction mixture is extracted with diethyl ether (2 x 150 ml), dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting brown oil is purified by chromatography using EtOAc: hexane (1:4 to pure EtOAc). This afforded a colorless oil (4.87g, 45%); GCMS
15 (EI) m/e 185 (M⁺), 170, 157, 142, 130, 112, 98, 84, 70, 56.

iii) **Ethyl-4-hydroxyazepane-1-carboxylate**

- Ethyl-4-oxoazepane-1-carboxylate (4.5 g, 24.7 mmol) and methanol (50 ml) are stirred at 0°C under argon. Sodium borohydride (934 mg, 24.7 mmol) is added in portions.
20 Reaction is allowed to warm to room temperature overnight. Reaction is quenched with 5% HCl aqueous solution and concentrated *in vacuo*. To the resulting liquid, washed with water and extracted with ethyl acetate. Organic layers are combined, dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting orange oil is purified by chromatography on silica gel using EtOAc: hexane (1:4 to pure EtOAc) as eluant to afford
25 the product as a colorless oil (2.98 g, 65%). ¹H NMR (300 MHz, CDCl₃): 4.18-4.08 (m, 2H), 3.95-3.85 (m, 1H), 3.51-3.31 (m, 3H), 2.05 (s, 1H), 2.05-1.61 (6H), 1.28 (s, 1H), 1.44-1.23 (m, 3H); LCMS (EI) m/e 210 (M + Na), 188 (M⁺), 170 (M - H₂O).

iv) **Ethyl-4-bromoazepane-1-carboxylate**

- 30 Triphenylphosphine (7.08g, 27 mmol) is added to a mixture of ethyl-4-hydroxyazepane-1-carboxylate (3.37 g, 18 mmol) in methylene chloride (180 ml) at 0°C under argon. Added carbon tetrabromide (8.95 g, 27 mmol), maintaining temperature at 0°C. Reaction mixture

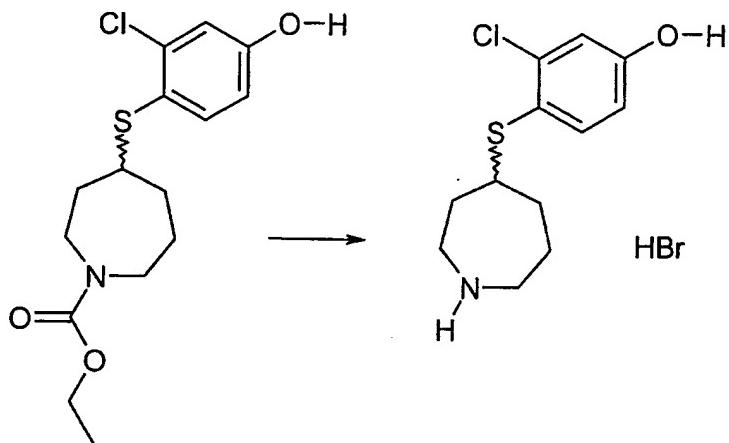
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is allowed to warm to room temperature and stirred for 18 hours. Concentrating reaction mixture *in vacuo* afforded a brown oil which is purified by chromatography using EtOAc: hexane (1:9 to 1:4) giving a colorless oil (3.38 g, 75%). ¹H NMR (300 MHz, CDCl₃): 4.4- 4.36 (m, 1H), 4.19- 4.11 (m, 2H), 3.57-3.38 (m, 4H), 2.28- 1.99 (m, 5H),
5 1.77- 1.73 (m, 1H), 1.29-1.24 (t, J = 7.14 Hz).

v) **Ethyl-4-[(2-chloro-4-hydroxyphenyl)thio]azepane-1-carboxylate**
Ethyl-4-bromoazepane-1-carboxylate (3.38g, 13.5 mmol), 2-chloro-4-hydroxythiophenol
10 (2.17 g, 13.5 mmol), potassium carbonate (5.6 g, 40.5 mmol) and dimethylformamide (87 ml) afforded a light yellow oil (3.50 g, 79%). ¹H NMR (300 MHz, CDCl₃): 7.4-7.34 (d, J = 18 Hz, 1 H), 6.99- 6.98 (d, J = 3 Hz, 1H), 6.74- 6.7 (d, J = 12 Hz, 1H), 4.23- 4.12 (m, 2H), 3.67- 3.25 (m, 5H), 1.98- 1.63 (m, 6H), 1.29- 1.25 (m 3H).

15 vi) **3-Chloro-4-[(1-methylazepan-4-yl)thio]phenol**
To a cooled solution of 1.0M lithium aluminium hydride in tetrahydrofuran (4 ml) is added ethyl-4-[(2-chloro-4-hydroxyphenyl)thio]azepane-1-carboxylate (600 mg, 1.8 mmol) in anhydrous tetrahydrofuran (6 ml) at 0°C under argon. After the reaction mixture is allowed to warm to room temperature overnight, cooled to 0°C and quenched slowly
20 with water (0.6 ml), then 15% NaOH aqueous solution (0.6 ml) and then water (1.2 ml). Stirred vigorously until a white precipitate is observed. The crude mixture is washed with brine (30 ml) and extracted with EtOAc (3 x 40 ml). Organic layers are combined, dried over sodium sulfate, filtered and concentrated *in vacuo* to give a yellow oil.
Chromatography of oil using a gradient elution from chloroform to 1:4 methanol:
25 chloroform afforded a yellow oil (330 mg, 67%). ¹H NMR (300 MHz, CDCl₃): 7.33-7.29 (d, J = 12 Hz, 1 H), 6.89 (s, 1H), 6.63-6.6 (d, J = 9 Hz, 1H), 4.21 (broad s, 1H), 3.39-3.78 (m, 1H), 2.88-2.81 (m, 2H), 2.7-2.68 (m, 2H), 2.45 (s, 3H), 2.15-2.04 (m, 2H), 1.86-1.63 (m, 4H); ¹³C NMR (300 MHz): 159, 139, 137, 120, 117, 115, 58, 54, 46, 45, 33, 31, 24;
LCMS: m/e 272 (M+H). TLC (20% methanol in chloroform, silica gel plate, iodine
30 stained) R_f 0.45.

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Example 15 (a)**4-(Azepan-4-ylthio)-3-chlorophenol hydrobromide**

Ethyl-4-[(2-chloro-4-hydroxyphenyl)thio]azepane-1-carboxylate (210 mg) is refluxed in

- 5 48% HBr aqueous solution (5.0 ml) overnight under argon. After concentration of
reaction mixture *in vacuo*, purification of an aliquot of the resulting brown residue (1/3 portion) by HPLC afforded a colorless oil (16 mg.) ¹H NMR (300 MHz, CD₃OD): 7.44-7.4 (d, *J* = 12 Hz, 1H), 6.92 (s, 1H), 6.74-6.70 (d, *J* = 12 Hz, 1H), 3.45-3.35 (m, 2H), 3.31-3.29 (m, 2H), 3.23-3.14 (m, 3H), 2.15-2.03 (m, 3H), 1.91-1.69 (m, 3H); ¹³C NMR (300 MHz) 160, 140, 139, 122, 118, 116, 47, 47, 43, 33, 31, 23; TLC (silica gel plate, 10 6:2:2 n-butanol: water: glacial acetic acid, iodine stained) R_f 0.6.

Example 15 (b)**(R)- 4-(Azepan-4-ylthio)-3-chlorophenol hydrobromide**

15

Example 15 (c)**(S)- 4-(Azepan-4-ylthio)-3-chlorophenol hydrobromide**

- Ethyl-4-[(2-chloro-4-hydroxyphenyl)thio]azepane-1-carboxylate (1.0g) is subjected to
20 chromatography on a 3578:CHIRALPAK-AD column eluting with hexane:ethanol (90:10 v/v) containing 0.2% DME. There is thus obtained 420 mg each of (R)- ethyl-4-[(2-

chloro-4-hydroxyphenyl)thio]azepane-1-carboxylate and (*R*)-ethyl-4-[(2-chloro-4-hydroxyphenyl)thio]azepane-1-carboxylate; retention times 6.8 minutes and 7.5 minutes. Each enantiomer is treated with 48% HBr aqueous solution as above to give the title compounds as pale yellow solids (250 mg).

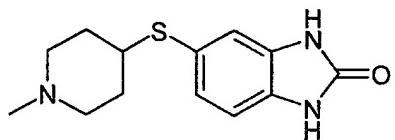
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Enantiomer 1: retention time 18.2 minutes [Chiralpak-AD (3538) eluting with hexane:ethanol (85:15 v/v) containing 0.2% DME]; LCMS 258 (100%, M+H), Rt = 2.4 min.

- 10 Enantiomer 2: retention time 20.8 minutes [Chiralpak-AD (3538) eluting with hexane:ethanol (85:15 v/v) containing 0.2% DME]; LCMS 258 (95%, M+H), Rt = 2.4 min.

Example 16

- 15 **5-[(1-methyl-4-piperidinyl)sulfanyl]-1,3-dihydro-2H-benzimidazol-2-one**



(i) 2-oxo-2,3-dihydro-1H-benzimidazole-5-sulfonyl chloride.

- 2,3-dihydro-1H-benzimidazol-2-one (J. Chem. Soc. Perkin I, 1982, 261-270), (6.7g, 20 50.0mmole), was stirred magnetically in dry dichloromethane (50ml). Chlorosulfonic acid (16.6ml, 250.0mmole) was added dropwise, at a rate that the solvent refluxed gently. Once the initial exotherm had subsided, the mixture was heated under gentle reflux for 17 to 18 hr. The cooled solution was poured onto ice. A white solid precipitated on stirring, this was filtered off, washed with water, dried at 60°C, under vacuum. Weight = 9.94g, 25 m.p. >260°C, m/z (FIANEGL.M.) = 231.1 [(M-H)].

(ii) S-(2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)ethanethioate.

- 2-oxo-2,3-dihydro-1H-benzimidazole-5-sulfonyl chloride (9.9g, 42.6mmole) was dissolved in a mixture of acetic acid (109ml) and acetic anhydride (35ml). With stirring, 30 sodium acetate (10.9g) was then added. This reaction mixture was cooled to 10°C, and

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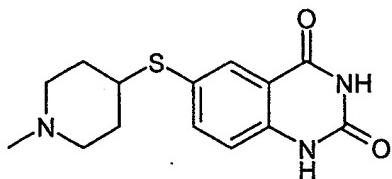
zinc dust (13.0g), was added in portions, keeping the temperature at between 10 and 20°C throughout additions. The mixture was then stirred at room temperature for 24hr. The mixture was evaporated *in vacuo*. The residue was slurried with chloroform and sodium bicarbonate solution, filtered, the filtered off solid was washed several times with
5 chloroform. The solid that remained was extracted into hot ethyl acetate several times, the ethyl acetate extracts were combined, washed with water, Rochelle's salt solution, dried with magnesium sulfate, filtered, evaporated *in vacuo*. Weight = 0.184g, m.p. = 258 °C.
¹H NMR, δH (300MHz; CD₃OD) 2.26-2.32 (3H, s, CH₃). 6.94-6.98 (3H, m+s, Ar-H); m/z (FIANEGLM) = 207.1 [(M-H)⁺]
10
(iii) 5-[(1-methyl-4-piperidinyl)sulfanyl]-1,3-dihydro-2H-benzimidazol-2-one.
S-(2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)ethanethioate (0.169g, 0.81mmole) was dissolved in dry DMF (5ml), with stirring. To this solution was added 1-methyl-4-piperidinyl methanesulfonate (0.174g, 0.90mmole) and caesium fluoride (0.137g,
15 0.90mmole). This solution was brought to 80°C, and pyrrolidine (0.075ml, 0.90mmole) was added. This reaction mixture was kept at this temperature for 22hr, under a nitrogen atmosphere. The reaction mixture was evaporated *in vacuo*, the residue was dissolved in chloroform and a little methanol, and filtered off from insoluble material. The filtrate was passed down acid ion-exchange material in a cartridge (5g, SCX-2). The cartridge was
20 washed with chloroform, and then methanol. The product was stripped off using 2M NH₃ in methanol. Fractions containing product were bulked, evaporated *in vacuo*. The residue was purified by preparative liquid chromatography. Fractions containing product were bulked, evaporated, passed down another SCX-2 cartridge to regenerate the free-base, evaporated *in vacuo*, then crystallised with diethyl ether to give the title compound as a
25 colourless solid (0.0369g). m.p. = 213.8-214.7 °C. ¹H NMR, δH (300MHz; CD₃OD) 1.48-1.70 (2H, m, 2 x C-H), 1.83-2.00 (2H, m, 2 x C-H), 2.05-2.15 (2H, m, 2 x C-H), 2.22-2.28 (3H, s, NCH₃), 2.80-2.88 (2H, m, 2 x C-H), 2.93-2.03 (1H, m, HCS), 7.00-7.05 (1H, d, Ar-H), 7.05-7.20 (1H, d, Ar-H; 1H, s, Ar-H), LCMS retention time ~0.848 min, m/z (GRADPL.M) = 264.1 [(M+H)⁺, 100%].

30

Example 17

6-[(1-methyl-4-piperidinyl)sulfanyl]-2,4(1H,3H)-quinazolinedione

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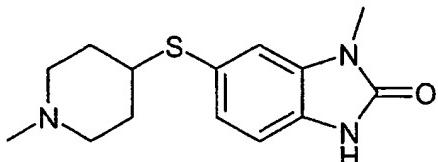
By proceeding in a similar manner to Example 16 but using 2,4(1H,3H)-quinazolininedione in place of 2,3-dihydro-1H-benzimidazol-2-one in step (i) there was prepared the title compound as a colourless solid.

- 5 m.p. >260°C. ^1H NMR, δH (300MHz; $(\text{CD}_3)_2\text{SO}$) 1.42-1.56 (2H, m, 2 x C-H), 1.82-1.92 (2H, m, 2 x C-H), 1.95-2.08 (2H, m, 2 x C-H), 2.12-2.18 (3H, s, NCH_3), 2.64-2.75 (2H, m, 2 x C-H), 3.05-3.18 (1H, m, HCS), 7.12-7.18 (1H, d, Ar-H), 7.65-7.70 (1H, d, Ar-H), 7.82-7.84 (1H, s, Ar-H), 11.20-11.50 (2H, 2 x s, 2 x NH); LCMS retention time ~0.832 min, m/z (GRADPL.M) = 292.1 [(M+H) $^+$, 100%].

10

Example 18

1-Methyl-6-[(1-methyl-4-piperidinyl)sulfanyl]-1,3-dihydro-2H-benzimidazol-2-one



(i) N-Methyl-5-[(1-methyl-4-piperidinyl)sulfanyl]-2-nitroaniline.

- 15 1-Methyl-4-piperidinethiol (J. Med. Chem. 1993, 36(22), 3261), (1.31g, 10.0mmole) was stirred in dry DMF (10ml). To this was added 60% sodium hydride–oil dispersion (0.4g, 10.0mmole), the mixture was stirred at ambient temperature for 1hr. To the white suspension of thiolate, 5-chloro-N-methyl-2-nitroaniline (Synth. Commun. 2000, 30(19), 3523-3526), (1.87g, 10.0mmole) was added. The stirred reaction mixture was heated to 20 60°C, under a nitrogen atmosphere, and kept at this temperature for 18hr. The reaction mixture was evaporated *in vacuo*, and the residue was dissolved in chloroform and washed with water, then brine. The organic extract was dried with magnesium sulfate, filtered, evaporated *in vacuo*. The residue was purified using flash chromatography, on silica-gel as stationary phase, and gradient elution with ammonia-methanol:dichloromethane (0 to 20%). Fractions containing product were bulked, evaporated *in vacuo*. Weight = 1.83g, m.p. = 90°C. ^1H NMR δH (300MHz; CDCl_3) 1.68-
- 25

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1.85 (2H, m, 2 x C-H), 2.05-2.20 (4H, m, 4 x C-H), 2.28-2.30 (3H, s, NCH₃), 2.78-2.88 (2H, m, 2 x C-H), 2.97-3.03 (3H, d, NCH₃), 3.25-3.40 (1H, m, HCS), 6.50-6.54 (1H, d, Ar-H), 6.68-6.70 (1H, s, Ar-H), 8.07-8.10 (1H, d, Ar-H), 8.10-8.20 (1H, s, NH); LCMS retention time ~2.349 min, m/z (GRADPL.M) = 282.1 [(M+H)⁺, 100%].

5

(ii) N²-Methyl-4-[(1-methyl-4-piperidinyl)sulfanyl]-1,2-benzendiamine.

N-Methyl-5-[(1-methyl-4-piperidinyl)sulfanyl]-2-nitroaniline (0.56g, 2.0mmole) was suspended in ethanol (30ml), and hydrogenated at 60 psi, in the presence of 5% palladium on charcoal (0.2g) for 1hr. The reaction mixture was filtered, evaporated *in vacuo*. Weight 10 = 0.427g of oil. LCMS retention time ~0.740 min, m/z (GRADPL.M) = 252.1 [(M+H)⁺, 100%].

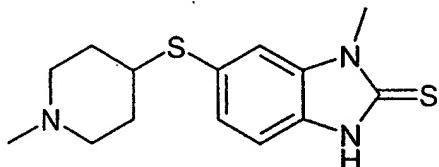
(iii) 1-Methyl-6-[(1-methyl-4-piperidinyl)sulfanyl]-1,3-dihydro-2H-benzimidazol-2-one

15 N²-Methyl-4-[(1-methyl-4-piperidinyl)sulfanyl]-1,2-benzendiamine (0.427g, 1.7mmole) and a solution of urea (0.105g, 1.75mmole) in water (2ml) were added to dimethyl acetamide (10ml). This reaction mixture was irradiated in a microwave oven, at 300 Watts and 180°C for a total of 3hr 6 min. The reaction mixture was evaporated *in vacuo*. The residue was dissolved in methanol and added to an acid ion-exchange material in a 20 cartridge (10g, SCX-2). The cartridge was washed with methanol. The product was stripped off using 2M NH₃ in methanol. Fractions containing product were bulked, evaporated *in vacuo*. The residue was purified by preparative liquid chromatography. Fractions containing product were bulked, evaporated, dissolved in methanol, passed down another SCX-2 cartridge to regenerate the free-base, evaporated *in vacuo*. The 25 residue was dissolved in chloroform, filtered, evaporated *in vacuo* and crystallised with diethyl ether to give the title compound as a colourless solid (0.0933g). m.p. = 196.4-197.6°C. ¹H NMR δH (300MHz; CDCl₃) 1.62-1.76 (2H, m, 2 x C-H), 1.90-2.08 (4H, m, 4 x C-H), 2.22-2.27 (3H, s, NCH₃), 2.80-2.98 (2H, m, 2 x C-H; 1H, m, HCS), 3.40-3.42 (3H, s, NCH₃), 6.93-7.00 (1H, d, Ar-H), 7.06-7.10 (1H, s, Ar-H), 7.18-7.21 (1H, d, Ar-H), 30 9.04-10.04 (1H, s, NH); LCMS retention time ~1.189 min, m/z (GRADPL.M) = 278.1 [(M+H)⁺, 100%].

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Example 19

1-Methyl-6-[(1-methyl-4-piperidinyl)sulfanyl]-1,3-dihydro-2H-benzimidazole-2-thione

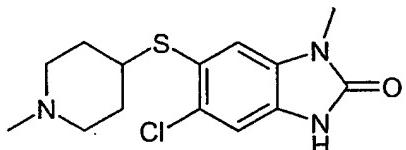


- 5 By proceeding in a similar manner to Example 18, but using thiourea in place of urea in step (iii) there was prepared the title compound as a colourless solid.
- ¹H NMR δH (300MHz; CDCl₃) 1.70-1.86 (2H, m, 2 x C-H), 1.90-2.08 (2H, m, 2 x C-H), 2.10-2.22 (2H, m, 2 x C-H), 2.22-2.30 (3H, s, NCH₃), 2.72-2.90 (2H, m, 2 x C-H), 3.05-3.15 (1H, m, HCS), 3.74-3.80 (3H, d, NCH₃), 6.70-6.75 (1H, d, Ar-H), 7.15-7.20 (1H, d, Ar-H; 1H, s, Ar-H); LCMS retention time ~1.903 min, m/z (GRADPL.M) = 294.1 [(M+H)⁺, 100%].
- 10

Ar-H; 1H, s, Ar-H); LCMS retention time ~1.903 min, m/z (GRADPL.M) = 294.1 [(M+H)⁺, 100%].

Example 20

5-Chloro-1-methyl-6-[(1-methyl-4-piperidinyl)sulfanyl]-1,3-dihydro-2H-benzimidazol-2-one.



- (i) **4-Chloro-N-methyl-5-[(1-methyl-4-piperidinyl)sulfanyl]-2-nitroaniline**
- By proceeding in a similar manner to Example 18 (i) but using 4,5-dichloro-N-methyl-2-nitroaniline (Synth. Commun. 2000, 30 (19), 3523-3526) in place of 5-chloro-N-methyl-2-nitroaniline, there was prepared the title compound as a yellow solid. m.p. = 102 °C.
- 20
- ¹H NMR δH (300MHz; CDCl₃) 1.77-1.92 (2H, m, 2 x C-H), 2.08-2.30 (4H, m, 4 x C-H), 2.30-2.34 (3H, s, NCH₃), 2.78-2.88 (2H, m, 2 x C-H), 2.98-3.04 (3H, d, NCH₃), 3.25-3.40 (1H, m, HCS), 6.58-6.60 (1H, s, Ar-H), 8.00-8.12 (1H, s, NH), 8.15-8.18 (1H, s, Ar-H); m/z (FIAPOS.L.M) = 316 [(M+H)⁺, 100%].

25

(ii) **4-Chloro-N¹-methyl-5-[(1-methyl-4-piperidinyl)sulfanyl]-1,2-benzenediamine**

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By proceeding in a similar manner to Example 18 (ii) there was prepared the title compound as an oil, (FIAPOL.M) = 316 [(M+H)⁺, 100%].

(iii) 5-Chloro-1-methyl-6-[(1-methyl-4-piperidinyl)sulfanyl]-1,3-dihydro-2H-

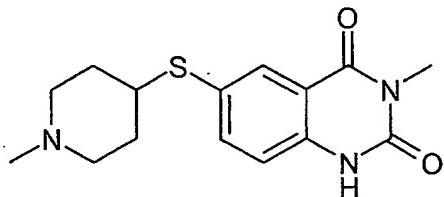
5 benzimidazol-2-one

4-Chloro-N¹-methyl-5-[(1-methyl-4-piperidinyl)sulfanyl]-1,2-benzenediamine (0.544g, 1.9mmole) was dissolved in dry THF (10ml), triethylamine (1.06ml, 7.6mmole) was added, and the reaction mixture was cooled to 0°C using an ice-salt bath. A solution of triphosgene (0.38g, 1.26mmole) in THF (10ml) was added, dropwise, such that the temperature was kept below 10°C. After additions were complete, the mixture was allowed to stir at ambient temperature for 1hr. The mixture was heated to boiling, and held at this temperature for 5 minutes. The reaction mixture was evaporated *in vacuo*. The residue was dissolved in chloroform, washed with water, and then added to an acid ion-exchange material in a cartridge (10g, SCX-2). The cartridge was washed with chloroform. The product was stripped off using 2M NH₃ in methanol. Fractions containing product were bulked, evaporated *in vacuo*. The residue was purified by preparative liquid chromatography. Fractions containing product were bulked, evaporated, passed down another SCX-2 cartridge to regenerate the free-base, evaporated *in vacuo*. The residue was crystallised with diethyl ether to give the title compound as a colourless solid (0.294g).

m.p. = 210.2-211.9°C. ¹H NMR δH (300MHz; CD₃OD) 1.61-1.75 (2H, m, 2 x C-H), 1.90-2.02 (2H, m, 2 x C-H), 2.08-2.25 (2H, m, 2 x C-H), 2.25-2.28 (3H, s, NCH₃), 2.80-2.90 (2H, m, 2 x C-H), 3.15-3.18 (1H, m, HCS), 3.35-3.42 (3H, s, NCH₃), 7.18-7.22 (1H, s, Ar-H), 7.32-7.35 (1H, s, Ar-H); LCMS retention time ~1.914 min, m/z (GRADPL.M) = 312.0 [(M+H)⁺, 100%].

Example 21

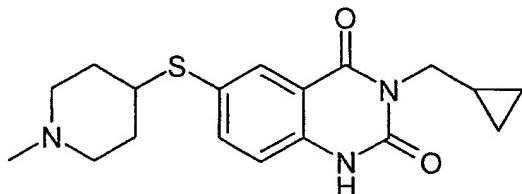
3-Methyl-6-[(1-methyl-4-piperidinyl)sulfanyl]-2,4(1H,3H)-quinazolinedione



60% oil dispersion of sodium hydride (0.032g, 0.8mmole) was added to a stirred suspension of 6-[(1-methyl-4-piperidinyl)sulfanyl]-2,4(1H,3H)-quinazolinedione (Example 2, 0.233g, 0.8mmole) in dry DMF (15ml), at ambient temperature. After 30 minutes, this was gently warmed until a clear solution was obtained. The solution was 5 cooled to 0°C, and dimethyl sulfate (0.085ml, 0.9mmole) was added, the reaction mixture was then allowed to stir at ambient temperature for 60 minutes. The solution was evaporated *in vacuo*, and the residue was dissolved in chloroform, washed with water, dried with magnesium sulfate, filtered, evaporated *in vacuo*. The residue was purified on a mass guided preparative liquid chromatography column to separate the mono-methylated 10 product from dimethylated material. A free-base of the mono-methylated material was obtained from the formate salt (the form it came off the column), by dissolving the residue in warm methanol and adding to an acid ion-exchange material in a cartridge (10g, SCX-2). The cartridge was washed with methanol. The product was stripped off 15 using 2M NH₃ in methanol. Fractions containing product were bulked and evaporated *in vacuo* to give the title compound as a colourless solid (0.016g) m.p. = 200.8-202.6°C. ¹H NMR δH (300MHz;CD₃OD) 1.58-1.72 (2H, m, 2 x C-H), 1.92-2.02 (2H, m, 2 x C-H), 2.12-2.24 (2H, m, 2 x C-H), 2.25-2.30 (3H, s, NCH₃), 2.80-2.91 (2H, m, 2 x C-H), 3.07- 20 3.22 (1H, m, HCS), 3.35-3.40 (3H, s, NCH₃), 7.13-7.17 (1H, d, Ar-H), 7.71-7.73 (1H, d, Ar-H), 8.05-8.08 (1H, s, Ar-H); LCMS retention time ~1.432 min, m/z (GRADPL.M) = 306.1 [(M+H)⁺, 100%].

Example 22

3-Cyclopropylmethyl-6-[(1-methyl-4-piperidinyl)-2,4(1H,3H)-quinazolinedione



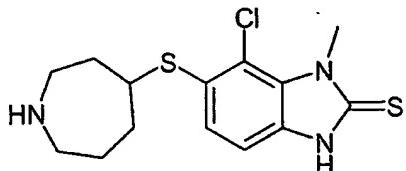
25 By proceeding in a similar manner to Example 21 but using cyclopropylmethyl chloride, there was prepared the title compound as a colourless solid. ¹H nmr, δH (300MHz; CDCl₃) 0.44-0.52 (4H, m, 4 x C-H), 1.28-1.40 (1H, m, C-H), 1.60-1.74 (2H, m, 2 x C-H), 1.92-2.12 (4H, m, 4 x C-H), 2.24-2.30 (3H, s, NCH₃), 2.76-2.88 (2H, m, 2 x C-H), 2.95-

-72-

3.10 (1H, m, HCS), 3.90-3.98 (2H, d, CH₂), 7.02-7.04 (1H, d, Ar-H), 7.62-7.66 (1H, d, Ar-H), 8.18-8.20 (1H, s, Ar-H); LCMS retention time ~2.630 min, m/z (GRADPL.M) = 346.1 [(M+H)⁺, 100%].

5 Example 23

6-(Azepan-4-ylsulfanyl)-7-chloro-1-methyl-1,3-dihydro-benzimidazole-2-thione



(i) 5-Oxo-azepane-1, 4-dicarboxylic acid diethyl ester

Solutions of boron trifluoride etherate (14.19 g, 12.7 ml, 100 mmol) and ethyl diazoacetate (14.83 g, 13.6 ml), each in anhydrous diethyl ether (12.4 ml), were added simultaneously over 45 min to a stirred solution of 4-oxo-piperidine-1-carboxylic acid ethyl ester (17.12 g, 15.15 ml, 100 mmol) and anhydrous diethyl ether (40 ml), maintaining temperature between -25°C and -33°C under and atmosphere of nitrogen.

After addition was completed, the mixture was stirred for an additional hour at -30°C and then allowed to warm to room temperature. There was then carefully added 30% potassium carbonate (200ml) and the mixture was extracted with ethyl acetate (3 × 40 ml). The combined organic phases were dried over magnesium sulfate, filtered and concentrated *in vacuo* to give a yellow oil (23.165 g, 90%). ¹H NMR (300MHz, CDCl₃): δ 4.26-4.08 (m, 4H), 3.9-3.73 (m, 3H), 3.52-3.4 (2H), 2.85-2.7 (m, 2H), 2.1-2.04 (m, 2H), 1.37-1.22 (6H).

(ii) 4-Oxo-azepane-1-carboxylic acid ethyl ester

5-Oxo-azepane-1,4-dicarboxylic acid diethyl ester (25 g, 97 mmol) was refluxed in 4N HCl (370 ml) for 6 hours under nitrogen. The mixture was allowed to cool to room temperature and stirred overnight. The reaction mixture was then concentrated *in vacuo* to afford a red oil which was treated with water (90 ml) and cooled to -5°C in MeOH / ice bath. There was then added portions of 30% aqueous potassium carbonate to pH = 11 and then ethyl chloroformate was added over 20 min maintaining the temperature at -5°C. The mixture was allowed to warm to 0°C and stirred for 2 hours. The mixture was then

allowed to warm to room temperature and stirred overnight. The reaction mixture extracted with diethyl ether (4×150 ml), dried over magnesium sulfate, filtrated and evaporated. The resulting brown oil was purified by silica gel chromatography using EtOAc: Hexane (20: 80). This afforded a yellow oil (8.73 g, 48%). ^1H NMR (300MHz, CDCl₃): δ 4.22-4.08 (m, 2H), 3.9-3.7 (m, 4H), 3.65-3.38 (2H), 2.8-2.7 (m, 2H), 2.1-2.04 (m, 2H), 1.35-1.22 (3H).

5 (iii) **4-Hydroxy-azepane-1-carboxylic acid ethyl ester**

4-Oxo-azepane-1-carboxylic acid ethyl ester (8 g, 43 mmol) and methanol (100 ml) were 10 stirred at 0°C under an atmosphere of nitrogen. Sodium borohydride (1.63 g, 43 mmol) was added in portions. The reaction mixture was stirred for 30min at 0°C, then allowed to warm to room temperature and stirred for one hour. The reaction was quenched with 5% HCl aqueous (20 ml) and concentrated *in vacuo*. The resulting oil was treated with water and extracted with diethyl ether (3×50 ml). The organic phases were combined, dried 15 over magnesium sulfate, filtrated and concentrated *in vacuo*. The resulting orange oil was purified by silica gel chromatography using EtOAc: Hexane (20: 80). This afforded a colorless oil (4.69 g, 58%). ^1H NMR (300MHz, CDCl₃): δ 4.31-4.08 (m, 2H), 3.9-3.8 (s, 1H), 3.55-3.28 (4H), 2.12-2.08 (m, 1H), 1.92-1.7 (m, 6H), 1.35-1.22 (3H).

20 (iv) **4-Bromo-azepane-1-carboxylic acid ethyl ester**

Triphenylphosphine (9.44 g, 36 mmol) was added to a mixture of 4-Hydroxy-azepane-1-carboxylic acid ethyl ester (4.5g, 24 mmol) in methylene chloride at 0°C under nitrogen. Carbon tetrabromide (11.93 g, 36 mmol) was added in portions, maintaining the 25 temperature at 0°C. The mixture was stirred at 0°C for 30min and then allowed to warm to room temperature. The reaction mixture was stirred for 18h at room temperature before concentrating the reaction mixture *in vacuo* to afford a brown oil, which was purified by silica gel chromatography using EtOAc: Hexane (20: 80 to 50:50). This afforded a colorless oil (3.1g, 51%). ^1H NMR (300MHz, CDCl₃): 4.28-4.34 (m, 1H), 4.02-4.18 (m, 2H), 3.4-3.6 (m, 4H), 2.01-2.39 (m, 6H), 1.7-1.86 (m, 1H), 1.23-1.39 (m, 3H).

30

(v) **4-Acetylsulfanyl-azepane-1-carboxylic acid ethyl ester**

- Potassium thioacetate (1.36 g, 12 mmol) and dry dimethylformamide (5 ml) were added to a solution of 4-bromo-azepane-1-carboxylic acid ethyl ester (1.5g, 6 mmol) in anhydrous tetrahydrofuran (50 ml). The reaction mixture was stirred for 18 hours at 60°C and concentration of the reaction mixture *in vacuo* afforded a yellow oil, which was purified by chromatography using EtOAc: Hexane (10: 90 to 40:60). This afforded a yellow oil (0.947 g, 65%). ¹H NMR (300MHz, CDCl₃): 4.02-4.21 (m, 2H), 3.5-3.69 (m, 2H), 3.21-3.5 (m, 4H), 2.21-2.28 (m, 2H), 2.1-2.18 (m, 2H), 1.65-1.82 (m, 4H), 1.23-1.32 (m, 3H).
- (vi) 4-(2-Chloro-3-methylamino-4-nitro-phenylsulfanyl)-azepane-1-carboxylic acid ethyl ester
4-Acetylsulfanyl-azepane-1-carboxylic acid ethyl ester (0.9 g, 3.7 mmol) and (2,3-dichloro-6-nitro-phenyl)-methyl-amine (0.811 g, 3.7 mmol) were dissolved in degassed methanol (50ml) at room temperature. 2M NaOH aqueous (3.7 ml, 7.4 mmol) was added in portions and the reaction mixture stirred for 2.5 hours at room temperature. Concentration of the reaction mixture *in vacuo* afforded a brown oil, which was purified by silica gel chromatography using EtOAc: Hexane (20: 80 to 50:50). This afforded the title compound as a colourless oil (1.086 g, 76%). ¹H NMR (300MHz, CDCl₃): 7.9-8 (m, 1H), 7.01 (s, 1H), 6.5-6.6 (m, 1H), 4.02-4.25 (m, 2H), 3.26-3.56 (m, 4H), 1.86-2.1 (m, 7H), 1.23-1.29 (m, 3H). LCMS retention time ~3.938 *m/z* 388 [(M+H)⁺, 97%].
- (vii) 4-(4-Amino-2-chloro-3-methylamino-phenylsulfanyl)-azepane-1-carboxylic acid ethyl ester
To a solution of 4-(2-chloro-3-methylamino-4-nitro-phenylsulfanyl)-azepane-1-carboxylic acid ethyl ester (1g, 2.6 mmol) in EtOAc (40 ml) was added tin chloride dihydrate (3.3 g, 12.9 mmol). The reaction mixture was heated to reflux and stirred for 1h. The reaction mixture was then allowed to cool down to room temperature and filtrated through a celite pad. Concentration of filtrate *in vacuo* afforded an orange oil, which was purified by silica gel chromatography using EtOAc: Hexane (20: 80). This afforded a yellow solid (0.512 g, 55%). ¹H NMR (300MHz, CDCl₃): 7.1-7 (m, 1H), 6.5-6.52 (m, 1H), 4.1-4.21 (m, 2H), 3.39-3.42 (m, 4H), 3.05-3.3 (m, 2H), 2.62-2.68 (m, 2H), 1.9-2.1 (m, 3H), 1.62-1.78 (m, 3H), 1.12-1.30 (m, 6H). LCMS retention time ~3.09 *m/z* 358 [(M+H)⁺, 72%].

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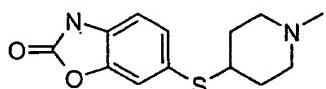
(viii) 4-(4-Chloro-3-methyl-2-thioxo-2,3-dihydro-1*H*-benzoimidazol-5-ylsulfanyl)-azepane-1-carboxylic acid ethyl ester

To a solution of 4-(4-amino-2-chloro-3-methylamino-phenylsulfanyl)-azepane-1-carboxylic acid ethyl ester (0.584 g, 1.63 mmol) and triethylamine (0.659 g, 6.52 mmol) in diethyl ether (30 ml) at -10°C was added thiophosgene in portions. The reaction mixture was stirred for one hour at -10°C, then allowed to warm to room temperature and stirred for one hour. Concentration of the reaction mixture *in vacuo* afforded a brown oil, which was purified using an SCX-2 cartridge. This afforded a brown oil (0.270 g, 41%).
¹H NMR (300MHz, CDCl₃): 7.4-7.5 (m, 1H), 7.1-7 (m, 1H), 4.1-4.18 (m, 6H), 3.46-3.55 (m, 4H), 3.2-3.35 (m, 2H), 1.6-1.7 (m, 2H), 1.62-1.78 (m, 3H), 1.12-1.30 (m, 3H). LCMS retention time ~3.71 *m/z* 400 [(M+H)⁺, 84%].

(ix) 6-(Azepan-4-ylsulfanyl)-7-chloro-1-methyl-1,3-dihydro-benzoimidazole-2-thione
 4-(4-chloro-3-methyl-2-thioxo-2,3-dihydro-1*H*-benzoimidazol-5-ylsulfanyl)-azepane-1-carboxylic acid ethyl ester (0.1 g, 0.25 mmol) was dissolved in 37% aqueous HBr and stirred at 80°C for 48h. Concentration of the reaction mixture *in vacuo* afforded colorless oil, which was cleaned up using an SCX-2 cartridge. The filtrate was concentrated *in vacuo* and purified by Mass Guided HPLC to give the title compound (0.027 g, 33%).
¹H NMR (300MHz, CDCl₃): 7.5-7.6 (s, 2H), 4.5-4.1 (m, 2H), 3.66-3.75 (m, 1H), 3.2-3.32 (m, 2H), 2.8-2.93 (m, 2H), 2.2-2.35 (m, 3H), 1.95-2.05 (m, 4H), 1.70-1.82 (m, 2H). LCMS retention time ~1.86 *m/z* 328 [(M+H)⁺, 95%].

Example 24

6-(1-Methyl-piperidin-4-ylsulfanyl)-3*H*-benzooxazol-2-one



25

(i) 2-Oxo-2,3-dihydro-benzooxazole-6-sulfonyl chloride

To an ice bath cooled stirred slurry of 3*H*-Benzooxazol-2-one (20g, 0.148mol) in dichloromethane (150cm³) was added chlorosulphonic acid (10cm³, 0.155mol) in two batches (1cm³ and 9cm³). After complete addition the ice bath was removed and after an

hour fine crystals started to form. The reaction mixture was filtered to yield 2-oxo-2,3-dihydro-benzooxazole-6-sulfonic acid (32g) as a fine purple solid. 12.5g of this solid was added to dichloromethane (80cm³) and treated with 2 equivalents of SOCl₂ (8.5cm³, 0.116mol). The reaction was heated to reflux for 2 hours then another 8 equivalents of 5 SOCl₂ was added, this was heated at reflux overnight and then treated with a few drops of DMF rapidly causing the completion of the reaction. The reaction was cooled to room temperature then poured onto stirred crushed ice. Filtration yielded 2-oxo-2,3-dihydro-benzooxazole-6-sulfonyl chloride as a fine grey solid (12.3g, 90%); ¹H NMR δ_H (300MHz; D6 DMSO) 7.00-7.10 (1H, m, 1 x Ar-H) and 7.38-7.49 (2H, m, Ar-H); LCMS 10 retention time ~ 3.7min, m/z (FIANEG) 231.9 [Cl³⁵(M)⁻, 100%] and 233.9 [Cl³⁷(M)⁻, 33%].

(ii) Thioacetic acid S-(3-acetyl-2-oxo-2,3-dihydro-benzooxazol-6-yl) ester

To an ice bath cooled, stirred mixture of 2-oxo-2,3-dihydro-benzooxazole-6-sulfonyl 15 chloride (12.2g, 52.2mmol), acetic acid (150cm³) and acetic anhydride (50cm³) was added sodium acetate (15g) followed by zinc powder (12g). The reaction was heated to 50°C overnight and another 12g of zinc was added. The reaction was left at room temperature for two days then concentrated *in vacuo* and triturated with water (3 x 50cm³). The solid that was formed was filtered off and dried *in vacuo* to yield thioacetic acid S-(3-acetyl-2-20 oxo-2,3-dihydro-benzooxazol-6-yl) ester as a dry grey solid (6.98g, 53%); ¹H NMR δ_H (300MHz; D6 DMSO) 2.48 (3H, s, one of COCH₃), 2.62 (3H, s, one of COCH₃), 7.31-7.39 (1H, m, Ar-H), 7.54 (1H, s, Ar-H) and 7.93-8.03 (1H, m, Ar-H).

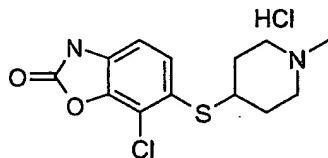
(iii) 6-(1-Methyl-piperidin-4-ylsulfanyl)-3H-benzooxazol-2-one

25 To a stirred mixture of thioacetic acid S-(3-acetyl-2-oxo-2,3-dihydro-benzooxazol-6-yl) ester (2.00g, 7.97mmol) and DMF was added methanesulfonic acid 1-methyl-piperidin-4-yl ester (2.3g, 12.0mmol), triphenylphosphine (1.04g, 3.99mmol) and K₂CO₃ (1.1g, 7.97mmol). This mixture was heated to 50°C under a flow of nitrogen, treated with pyrrolidine (1.33cm³, 15.9mmol) and then heated to 70°C overnight. A further portion of 30 methanesulfonic acid 1-methyl-piperidin-4-yl ester (1.5g) was added. After a further 3 hours at 70°C, the reaction was concentrated *in vacuo*, treated with 1N HCl (50ml) and the aqueous layer washed with CHCl₃ (50ml). The aqueous layer was filtered and then

basified using 2N NaOH, before being extracted with CHCl₃ (3 X 50ml) The combined organics were dried (MgSO₄) and concentrated *in vacuo* (and the residue purified by Prep-LCMS (mass guided). The solution returned was passed through a SCX ion exchange cartridge and concentrated *in vacuo* to yield the title compound (57mg) as
 5 colourless solid; ¹H NMR δ_H (300MHz; CDCl₃) 1.53-1.70 (2H, m, 2 x one of CH₂), 1.90-2.13 (4H, m, 4 x one of CH₂), 2.27 (3H, s, NCH₃), 2.81-2.97 (3H, m, HCS and 2 x NCH), 6.80-6.87 (1H, m, Ar-H) and 7.20-7.29 (2H, m, 2 x Ar-H).

Example 25

10 **7-Chloro-6-(1-methyl-piperidin-4-ylsulfanyl)-3H-benzooxazol-2-one hydrochloride salt**



(i) 2-Chloro-3-fluoro-6-nitro-phenol

2-chloro-3-fluoro-6-nitro-phenol was prepared using a literature procedure from 2-chloro-1,3-difluoro-4-nitro-benzene. (Hayakawa, Isao; Hiramitsu, Tokiyuki; Tanaka, Yoshiaki; Chem.Pharm.Bull.; 32; 12; 1984; 4907-4913).

(ii) 2-Chloro-3-(1-methyl-piperidin-4-ylsulfanyl)-6-nitro-phenol

A 60% dispersion of sodium hydride in mineral oil (532mg, 13.3mmol) was pre-washed 20 with 40-60 petroleum ether before use. To a solution of 1-methyl-piperidine-4-thiol (J. Med. Chem.; 36(22); 1993; 3261) (750mg, 6.05mmol) in DMF was added 2-chloro-3-fluoro-6-nitro-phenol (1.39g, 7.26mmol) as a solution in DMF under a flow of nitrogen forming a strong red solution. This was treated with washed sodium hydride (1 eq) and the reaction was slowly warmed to 60°C and then after 10 minutes concentrated *in vacuo* 25 to a orange oil. This was diluted with CHCl₃ (100cm³), H₂O (50cm³) and 2N NaOH (10cm³). The aqueous was isolated and washed with more CHCl₃ (50ml) before being acidified to pH ~4 using 2N HCl. The resultant solid was filtered off and dried *in vacuo* before being triturated with methanol to give the title compound as a yellow powder

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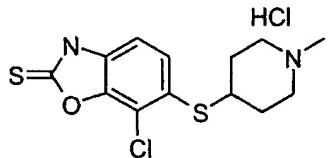
(915mg, 42%); LCMC retention ~2.72min, m/z (FIAPOS) 303.0 [Cl^{35} ($\text{M}+\text{H}$)⁺, 100%] and 305.0 [Cl^{37} ($\text{M}+\text{H}$)⁺, 33%].

- (iii) 6-Amino-2-chloro-3-(1-methyl-piperidin-4-ylsulfanyl)-phenol hydrochloride salt**
- 5 A slurry of 2-chloro-3-(1-methyl-piperidin-4-ylsulfanyl)-6-nitro-phenol (910mg, 3mmol) in methanol (20ml) and 10% ethanolic HCl (20ml) was treated with 5% Pd/C (500mg). This mixture was placed under a pressurised atmosphere of hydrogen gas (60 PSI) at room temperature for one hour. The reaction was filtered through a short pad of celite® and concentrated *in vacuo* to yield 6-amino-2-chloro-3-(1-methyl-piperidin-4-ylsulfanyl)-
- 10 phenol hydrochloride salt (925mg, ~99%) as a purple crystalline solid; ¹H NMR δ_{H} (300MHz; D4 methanol) 1.80-2.45 (6H, m, 3 x CH_2), 2.85-2.96 (3H, m, NCH_3), 3.10-3.25 (1H, m, SCH), 3.50-3.70 (2H, m, 2 x NCH) and 7.18-7.40 (2H, m, 2 x Ar-H); LCMC retention ~0.8min, m/z (FIAPOS) 273.0 [Cl^{35} ($\text{M}+\text{H}$)⁺, 100%] and 275.1 [Cl^{37} ($\text{M}+\text{H}$)⁺, 33%].
- 15
- (iv) 7-Chloro-6-(1-methyl-piperidin-4-ylsulfanyl)-3*H*-benzooxazol-2-one hydrochloride salt**
- 6-Amino-2-chloro-3-(1-methyl-piperidin-4-ylsulfanyl)-phenol hydrochloride salt was desalted by passing through a SCX ion exchange cartridge to yield 6-amino-2-chloro-3-
- 20 (1-methyl-piperidin-4-ylsulfanyl)-phenol (456mg, 1.67mmol) as an orange oil. This was dissolved in a mix of triethylamine (340mg, 3.35mmol) and tetrahydrofuran (10ml) cooled in an ice bath and then treated with triphosgene (200mg). After 1 hour, the reaction mixture was warmed to room concentrated, treated with 5g silica gel and concentrated *in vacuo*. The residue was purified using flash chromatography on silica (CH_2Cl_2 : methanolic ammonia 99:1) to yield a solid. This was treated with methanol (10ml) and a few drops of 10% HCl in ethanol until pH 1.0 and then concentrated *in vacuo* to yield the title compound as a purple solid (226mg, 45%); ¹H NMR δ_{H} (300MHz; D6 DMSO) 1.70-2.29 (6H, m, 6 x one of CH_2), 2.60-2.79 (3H, m, NCH_3), 2.85-3.00 (1H, m, HCS), 3.1-3.3 (2H, m, 2 x NCH), 7.01-7.11 (1H, m, Ar-H), 7.39-7.49 (1H, m, Ar-H) and 10.40-10.72 (1H, m, NH); LCMS retention time ~ 2.2 min, m/z (FIPOSES) 299.1 [Cl^{35} ($\text{M}+\text{H}$)⁺, 100%] and 301.1 [Cl^{37} ($\text{M}+\text{H}$)⁺, 33%].

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Example 26

7-Chloro-6-(1-methyl-piperidin-4-ylsulfanyl)-3H-benzooxazole-2-thione hydrochloride salt

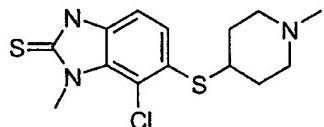


- 5 By proceeding in a similar manner to Example 25 but using thiophosgene in place of phosphogene in step (iv), there was prepared the title compound as a yellow solid. ^1H NMR δ_{H} (300MHz; D4 Methanol) 1.51-2.03 (6H, m, 6 x one of CH_2), 2.66 (3H, s, NCH_3), 2.8-2.9 (1H, m, HCS), 3.2-3.4 (2H, m, 2 x NCH), 6.90-6.98 (1H, m, Ar-H) and 7.33-7.42 (1H, m, Ar-H); LCMS retention time ~ 2.7 min, m/z (FIAPOSES) 315.0 [Cl^{35} ($\text{M}+\text{H}$) $^+$, 100%] and 317.0 [Cl^{37} ($\text{M}+\text{H}$) $^+$, 33%].
- 10

Example 27

7-Chloro-1-methyl-6-(1-methyl-piperidin-4-ylsulfanyl)-1,3-dihydro-benzimidazole-2-thione

15



(i) [2-Chloro-3-(1-methyl-piperidin-4-ylsulfanyl)-6-nitro-phenyl]-methyl-amine

- To a solution of (2,3-dichloro-6-nitro-phenyl)-methyl-amine (1.49g, 6.75mmol) in DMF was added NaH (60% dispersion in mineral oil) (198mg, 4.95mmol) followed by 1-methyl-piperidine-4-thiol (J. Med. Chem.; 36(22); 1993; 3261) (837mg, 6.41mmol). This mixture was stirred at room temperature for 10 minutes and then concentrated *in vacuo*. The residue was purified using flash chromatography on silica gel (35g) (98:2 to 85:15, CH_2Cl_2 : methanolic ammonia) yielding [2-chloro-3-(1-methyl-piperidin-4-ylsulfanyl)-6-nitro-phenyl]-methyl-amine (930mg); ^1H NMR δ_{H} (300MHz; CDCl_3) 1.72-1.91 (4H, m, 2 x CH_2), 2.05-2.23 (2H, m, 1 x CH_2), 2.30 (3H, s, CHNCH_3), 2.80-2.90 (2H, m, 2 x
- 20

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NCH), 3.10-3.15 (3H, m, CNCH₃) 3.25-3.38 (1H, m, SCH), 6.61-6.70 (1H, m, Ar-H), 7.25 (1H, s, Ar-H) and 7.89-7.94 (1H, m, Ar-H).

(ii) 3-Chloro-N²-methyl-4-(1-methyl-piperidin-4-ylsulfanyl)-benzene-1,2-diamine

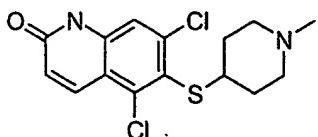
- 5 To a mixture of SnCl₂.2H₂O (1.33g) and ethyl acetate was added [2-chloro-3-(1-methyl-piperidin-4-ylsulfanyl)-6-nitro-phenyl]-methyl-amine (930mg, 2.95mmol). The reaction was stirred at room temperature overnight, treated with another equivalent of SnCl₂.2H₂O (665mg) and heated to 50°C. After a further 18hrs the reaction was concentrated *in vacuo* and then purified using flash chromatography on silica gel (35g) (98:2 to 80:10, CH₂Cl₂ : methanolic ammonia) yielding 3-chloro-N²-methyl-4-(1-methyl-piperidin-4-ylsulfanyl)-benzene-1,2-diamine.
- 10

(iii) 7-Chloro-1-methyl-6-(1-methyl-piperidin-4-ylsulfanyl)-1,3-dihydro-benzoimidazole-2-thione

- 15 To an ice cooled solution of 3-chloro-N²-methyl-4-(1-methyl-piperidin-4-ylsulfanyl)-benzene-1,2-diamine (560mg, 1.96mmol) in pyridine (309mg, 3.92mmol) and CH₂Cl₂ (10ml) was added thiophosgene (225mg, 1.96mmol). After 4 hours the reaction was concentrated *in vacuo* and then purified using flash chromatography on silica gel (35g) (98:2 to 85:15, CH₂Cl₂ : methanolic ammonia) yielding a solid which was triturated with
- 20 diethyl-ether, filtered, and the filtrate concentrated *in vacuo* to yield the title compound as a yellow solid (303mg, 47%); ¹H NMR δ_H (300MHz; CDCl₃) 1.62-2.20 (6H, m, 6 x one of CH₂), 2.32 (3H, m, CHNCH₃), 2.85-3.00 (2H, m, 2 x NCH), 3.05-3.15 (1H, m, HCS), 4.18 (3H, s, NCH₃), 6.94-7.03 (1H, m, Ar-H), 7.25 (1H, s, Ar-H) and 7.37-7.41 (1H, m, Ar-H); LCMS retention time ~ 1.7 min, m/z (FIAPOSES) 328.1 [Cl³⁵ (M+H)⁺, 100%]
- 25 and 330.1 [Cl³⁷ (M+H)⁺, 33%].

Example 28

5,7-Dichloro-6-(1-methyl-piperidin-4-ylsulfanyl)-1*H*-quinolin-2-one



(i) 4-(2,6-Dichloro-4-nitro-phenylsulfanyl)-1-methyl-piperidine

To a solution of 1,2,3-trichloro-5-nitro-benzene (1.53g, 6.75mmol) in DMF was added NaH (60% dispersion in mineral oil) (198mg, 4.95mmol) followed by 1-methyl-piperidine-4-thiol (J. Med. Chem.; 36(22); 1993; 3261) (837mg, 6.41mmol). This mixture was stirred at room temperature for 10 minutes and then concentrated *in vacuo*. The residue was purified using flash chromatography on silica gel (35g) (98:2 to 85:15, CH₂Cl₂ : methanolic ammonia) yielding 4-(2,6-dichloro-4-nitro-phenylsulfanyl)-1-methyl-piperidine (1.26g); ¹H NMR δ_H (300MHz; CDCl₃) 1.70-1.90 (4H, m, 2 x CH₂), 2.02-2.12 (2H, m, 1 x CH₂), 2.25 (3H, s, NCH₃), 2.70-2.80 (2H, m, 2 x NCH), 3.30-3.42 (1H, m, SCH) and 8.20 (2H, m, 2 x Ar-H).

(ii) 3,5-Dichloro-4-(1-methyl-piperidin-4-ylsulfanyl)-phenylamine

To a mixture of SnCl₂.2H₂O (1.77g) and ethyl acetate was added 4-(2,6-dichloro-4-nitro-phenylsulfanyl)-1-methyl-piperidine (1.26g, 3.92mmol). The reaction was stirred at room temperature overnight and then heated to 50°C. After 18 hours the reaction was complete and product was isolated using SCX-2 ion exchange cartridges yielding 3,5-dichloro-4-(1-methyl-piperidin-4-ylsulfanyl)-phenylamine.

20 (iii) 5,7-Dichloro-6-(1-methyl-piperidin-4-ylsulfanyl)-1*H*-quinolin-2-one

To a slurry of 3,5-dichloro-4-(1-methyl-piperidin-4-ylsulfanyl)-phenylamine (1 eq) in CH₂Cl₂ (10ml) and pyridine (1.5cm³) was added 3-ethoxy-acryloyl chloride (1 eq. 527mg, 3.9mmol) (synthesised from ethoxy-ethene according to the literature procedure of Fernandez, Franco; Garcia-Mera, Xerardo; Morales, Melvin; Rodriguez-Borges, Jose E.; Synthesis; 2; 2001; 239-242. After stirring at room temperature for one hour, the reaction was concentrated *in vacuo* to remove excess pyridine then treated with concentrated H₂SO₄ (2cm³). The reaction was quenched using 2M NaOH and diluted with CH₂Cl₂ (50ml). The organic layer was concentrated *in vacuo* and then purified using flash chromatography on silica (35g) (98:2 to 85:15, CH₂Cl₂ : methanolic ammonia) yielding a

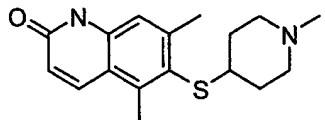
-82-

- solid which was triturated with diethyl-ether to form a powder which was filtered then dried *in vacuo* to yield the title compound (77mg); ^1H NMR δ_{H} (300MHz; D6 DMSO) 1.50-2.00 (6H, m, 6 x one of CH_2), 2.12 (3H, m, NCH_3), 2.61-2.78 (2H, m, 2 x NCH), 3.07-3.20 (1H, m, HCS), 6.60-6.70 (1H, m, Ar-H), 7.50 (1H, s, Ar-H), 8.05-8.15 (1H, m, 5 Ar-H) and 12.1 (1H, br. s, NH); LCMS retention time ~ 2.9 min, m/z (FIAPOSES) 343.0 [Cl^{35} & Cl^{35} ($\text{M}+\text{H}$) $^+$, 100%] and 345.0 [Cl^{35} & Cl^{37} ($\text{M}+\text{H}$) $^+$, 66%].

Example 29

5,7-Dimethyl-6-(1-methyl-piperidin-4-ylsulfanyl)-1*H*-quinolin-2-one

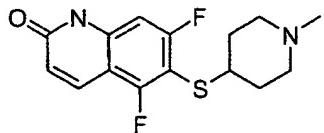
10



- By proceeding in a similar manner to Example 28 but using 1-chloro-2,3-dimethyl-4-nitro-benzene in place of 1,2,3-trichloro-5-nitro-benzene in step (i), there was prepared the title compound as a colourless solid. ^1H NMR δ_{H} (300MHz; CDCl_3) 1.61-2.00 (6H, m, 6 x one of CH_2), 2.22 (3H, m, NCH_3), 2.63-2.90 (9H, m, 2 x CH_3 , HCS and 2 x CH_3NCH), 6.64-6.75 (1H, m, Ar-H), 7.20 (1H, s, Ar-H), 8.0-8.10 (1H, m, Ar-H) and 15 12.0 (1H, br. s, NH); LCMS retention time ~ 2.8 min, m/z (FIAPOSES) 303.1 [($\text{M}+\text{H}$) $^+$, 100%].

Example 30

20 **5,7-Difluoro-6-(1-methyl-piperidin-4-ylsulfanyl)-1*H*-quinolin-2-one**



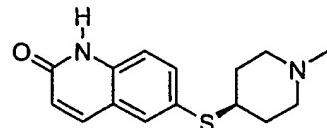
- By proceeding in a similar manner to Example 28 but using 1,2,3-trifluoro-5-nitro-benzene in place of 1,2,3-trichloro-5-nitro-benzene in step (i), there was prepared the title compound as a colourless solid. ^1H NMR δ_{H} (300MHz; D6 DMSO) 1.39-1.51 (4H, m, 4 x one of CH_2), 1.71-1.98 (2H, m, 2 x one of CH_2), 2.10 (3H, m, NCH_3), 2.60-2.70 (2H, m, 2 x CH_3NCH), 2.90-3.00 (1H, m, HCS), 6.59-6.69 (1H, m, Ar-H), 6.92-7.04 (1H, m,

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Ar-H), 7.90-7.98 (1H, m, Ar-H) and 12.1 (1H, br. s, NH); LCMS retention time ~ 2.4 min, m/z (FIAPOSES) 311.1 [(M+H)⁺, 100%].

Example 31

5 **6-(1-methyl-piperidin-4-ylsulfanyl)-1*H*-quinolin-2-one**



(i) **2-Oxo-1,2-dihydro-quinoline-6-sulfonyl chloride**

To an ice bath cooled stirred slurry of 2-hydroxyquinoline (30.5g, 0.210mol) in dichloromethane (300cm³) was added chlorosulphonic acid (70cm³, 1.05mol) in 4 equal sized batches. This was left to stir at room temperature for 2 days then slowly poured onto crushed ice. Large amount of a white solid formed in the lower chlorinated layer. This was filtered off and dried *in vacuo* to yield 2-Oxo-1,2-dihydro-quinoline-6-sulfonyl chloride as a dry white solid (36.3g); δ_H (300MHz; D6 DMSO) 6.51-6.59 (1H, m, 1 x Ar-H), 7.29-7.34 (1H, m, Ar-H), 7.71-7.79 (1H, m, Ar-H), 7.90-7.96 (1H, m, Ar-H) and 8.00-8.06 (1H, m, Ar-H); LCMS retention time ~ 3.43min, m/z (FIANEG) 241.9 [Cl³⁵(M)⁻, 100%] and 244.0 [Cl³⁷(M)⁻, 33%]. NMR and LCMS showed that this material contained some starting material as a minor impurity but no further purification was performed.

20 (ii) **Thioacetic acid *S*-(2-oxo-1,2-dihydro-quinolin-6-yl) ester**

To an ice bath cooled, stirred mixture of impure 2-Oxo-1,2-dihydro-quinoline-6-sulfonyl chloride (20g, ~82mmol), acetic acid (240cm³) and acetic anhydride (80cm³) was added sodium acetate (24g) in three equal sized batches. Then zinc powder (20g) was added in small batches (exothermic reaction). After one hour the ice bath was removed and the reaction was left stirring at room temperature for five days then concentrated *in vacuo* then triturated with water (~200cm³). The solid that was formed was filtered off and dried *in vacuo* to yield thioacetic acid *S*-(2-oxo-1,2-dihydro-quinolin-6-yl) ester as a dry grey solid (11.7g, ~65%); δ_H (300MHz; D6 DMSO) 2.42 (3H, s, COCH₃), 6.51-6.57 (1H, m, Ar-H), 7.32-7.37 (1H, m, Ar-H), 7.43-7.48 (1H, m, Ar-H), 7.72 (1H, s, Ar-H), 7.88-

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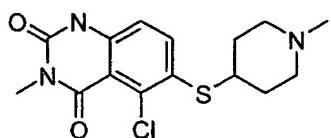
7.92 (1H, m, Ar-H) and 11.95 (1H, br s, N-H); LCMS retention time ~ 3.03min, m/z (FIAPOS) 220 [(M+H)⁺, 100]

(iii) 6-(1-methyl-piperidin-4-ylsulfanyl)-1*H*-quinolin-2-one

- 5 By proceeding in a similar manner to Example 24 but using thioacetic acid *S*-(2-oxo-1,2-dihydro-quinolin-6-yl) ester in step (i), there was prepared the title compound as a colourless solid. ¹H NMR δ_H (300MHz; CDCl₃) 1.53-1.70 (2H, m), 1.90-2.13 (4H, m), 2.27 (3H, s), 2.81-2.97 (3H, m), 6.62-6.70 (1H, m), 7.20-7.27 (1H, m), 7.50-7.56 (1H, m), 7.62-7.64 (1H, m) and 7.70-7.73 (1H, m),
 10 FIA-MS: 275 [(M+H)⁺, 100%]

Example 32

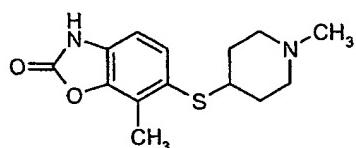
5-Chloro-3-methyl-6-(1-methyl-piperidin-4-ylsulfanyl)-1*H*-quinazoline-2,4-dione



- By proceeding in a similar manner to Example 25 but using N-methyl-2,3-dichloro-6-nitro-benzenecarboxamide in step (ii) there was prepared the title compound as a colourless solid. δ_H (300MHz; CDCl₃) 1.72 (2H, m), 1.95 (2H, m), 2.10 (2H, m), 2.30 (3H, s), 2.80 (2H, m), 3.18 (1H, m), 3.45 (3H, s), 7.01 (1H, d), 7.70 (1H, d), LCMS retention time ~ 1.18 min, m/z (FIAPOS) 340 [(M+H)⁺, 100].

20 Example 33

7-Methyl-6-(1-methyl-piperidin-4-ylsulfanyl)-3*H*-benzooxazol-2-one



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(i) 7-Methyl-3*H*-benzooxazol-2-one-6-sulfonic acid

7-Methyl-3*H*-benzooxazol-2-one [5.0g, 33 mmol, prepared according to the procedure described in J. Org. Chem. (1982), 47(14), 2804-6] was treated with chlorosulphonic acid as described in Example 9 (i) to give the title compound as an off- white solid (4.5g,

5 60%).

δ_H (300MHz, DMSO) 2.50 (s, 3H), 6.83 (d, 1H), 7.58 (d, 1H), 11.60 (brs, 1H).

(ii) 7-Methyl-6-(1-methyl-piperidin-4-ylsulfanyl)-3*H*-benzooxazol-2-one

A mixture of 7-methyl-3*H*-benzooxazol-2-one-6-sulfonic acid (2.5g, 11 mmol),

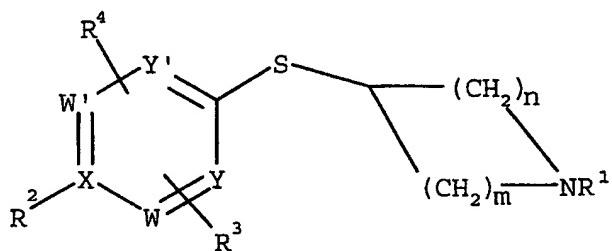
10 triphenylphosphine (13g, 50 mmol) and benzene (100 mL) was heated at reflux for 2h under Dean and Stark conditions. The reaction was cooled and treated with iodine (5g, 20 mmol) in small portions. The reaction was heated to reflux for a further 48h before being cooled and washed with 2.0M aqueous sodium hydroxide (2 X 20 ml). The combined aqueous extracts were washed with chloroform (2 X 50ml) and acidified to pH 4 with 15 concentrated hydrochloric acid. The resultant solid was collected and dried to yield a white solid which was used directly in the next step.

This material was treated with methanesulfonic acid 1-methyl-piperidin-4-yl ester according to the procedure described in Example 9 (iii). There was thus obtained the title compound as a colourless solid.

20 δ_H (300MHz; D4 methanol) 6.96 (1H, d), 7.40 (1H, d), 3.50 (2H, m), 3.35 (1H,m), 3.30 (3H, s), 3.15 (1H, m), 3.00 (2H, m), 2.50 (3H, s), 2.15 (2H, m), 1.80 (2H, m), FIA-MS: 279 [(M+H)⁺, 100%

Claims:

1. A method of treatment of a condition indicating treatment with a beta 4 subtype
 5 selective nicotinic acetylcholine receptor modulator comprising administering an effective amount of a compound represented by Formula (I) or pharmaceutically acceptable salts thereof:

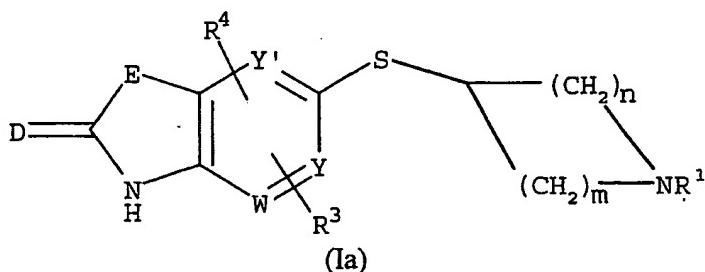


(I)

wherein:

- 10 R¹ is -H,
 C₁₋₁₂alkyl optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxyl, thiol, C₁₋₄alkoxy or C₁₋₄alkylthio, or aryl-C₁₋₄alkyl;
- 15 R² is -H,
 -OH,
 -C(O)-NH₂,
 -NH₂,
 -NH-Q-V-T, wherein Q is -C(O)-, -C(O)-NH-, -C(O)O-, or -SO₂-;
 V is H, aryl, aryl-C₁₋₁₂alkyl, diaryl-C₁₋₁₂alkyl, lactonyl, or C₁₋₁₈alkyl optionally substituted with halogen, hydroxyl, C₁₋₄alkoxy, -C(O)OC₁₋₄alkyl, -OC(O)C₁₋₄alkyl, aryl-C₁₋₄alkoxy, aryloxy, or SO₂C₁₋₄alkyl; and
 T is H, halogen, C₁₋₅alkyl, C₁₋₄alkoxy, nitro, aryl, aryl-C₁₋₄alkyl, or aryloxy unless V is H in which case T is absent; or
- 20
- 25

linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ia)



wherein D is O or S; and

E is O, S, NR⁵, C(R⁵)₂, O-CR⁵₂, NR⁵-CR⁵₂,

NR⁵-CO, CR⁵₂-O, CR⁵₂-S(O)_r, CR⁵₂-NR⁵,

CR⁵₂-CR⁵₂, CO-NR⁵, or CR⁵=CR⁵;

unless X is N in which case R² is absent

R³ is H, halogen, C₁₋₄alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF₃, OC₁₋₄alkyl, aryloxy, arylC₁₋₄alkyl, arylC₁₋₄alkoxy, C₃₋₁₀cycloalkoxy, carboxy, carbonamido, -CO-, -CO₂H, -NH₂, NH-C₁₋₄alkyl, aryl, hydroxy, -SO₂NH₂, -SO₂NHC₁₋₄alkyl, or -C₁₋₄alkyl-OH;

R⁴ is H, halogen, C₁₋₄alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF₃, OC₁₋₄alkyl, aryloxy, arylC₁₋₄alkyl, arylC₁₋₄alkoxy, C₃₋₁₀cycloalkoxy, carboxy, carbonamido, -CO-, -CO₂H, -NH₂, NH-C₁₋₄alkyl, aryl, hydroxy, -SO₂NH₂, -SO₂NHC₁₋₄alkyl, or -C₁₋₄alkyl-OH;

R⁵ is each independently H or C₁₋₄alkyl;

X is C or N;

W is C or N;

W' is C or N;

Y is C or N;

Y' is C or N;

provided that there are no more than two N atoms in the aryl ring;

m is 1, 2, or 3;

n is 1, 2, or 3; and

the sum of m and n is 2, 3, 4, 5, or 6;

provided that

when X, W, W', Y and Y' are all C, R³ and R⁴ are H and R¹ is selected from H, unsubstituted C₁₋₄alkyl and unsubstituted C₃₋₄cycloalkyl, R² may not be -OH; and that

5 when one of X, Y and Y' is N, R³ and R⁴ are H and R¹ is selected from H, unsubstituted C₁₋₄alkyl and unsubstituted C₃₋₄cycloalkyl, R² may not be H.

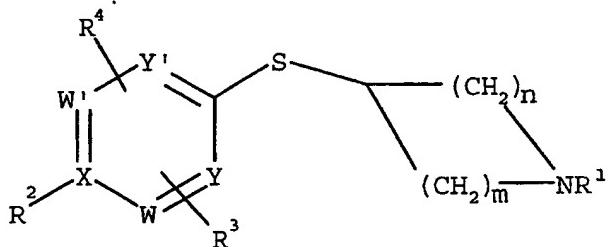
2. The method of claim 1

provided that

10 when X, W, W', Y and Y' are all C and R³ and R⁴ are H, R² may not be -OH; and that

when one of X, Y and Y' is N and R³ and R⁴ are H, R² may not be H.

3. A method of treatment of dysfunctions of the central and autonomic nervous systems comprising administering an effective amount of a compound represented by Formula (I) or pharmaceutically acceptable salts thereof:



(I)

wherein:

20 R¹ is -H,
C₁₋₁₂alkyl optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxyl, thiol, C₁₋₄alkoxy or C₁₋₄alkylthio, or aryl-C₁₋₄alkyl;

R² is -H,
-OH,
-C(O)-NH₂,

25

-NH₂,

-NH-Q-V-T, wherein

Q is -C(O)-, -C(O)-NH-, -C(O)O-, or -SO₂-;

V is H, aryl, aryl-C₁₋₁₂alkyl, diaryl-C₁₋₁₂alkyl, lactonyl, or C₁₋₁₈alkyl optionally substituted with halogen, hydroxyl, C₁₋₄alkoxy, -

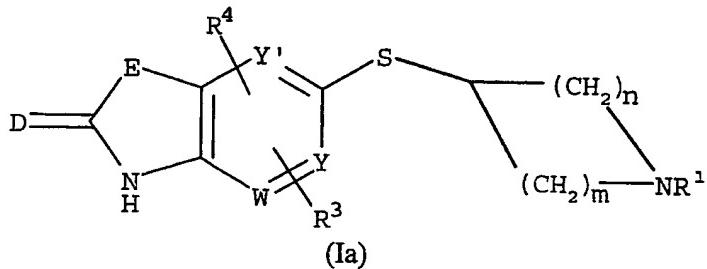
C(O)OC₁₋₄alkyl, -OC(O)C₁₋₄alkyl, aryl-C₁₋₄alkoxy, aryloxy, or SO₂C₁₋₄alkyl; and

T is H, halogen, C₁₋₅alkyl, C₁₋₄alkoxy, nitro, aryl, aryl-C₁₋₄alkyl, or aryloxy unless V is H in which case T is absent; or

5

10

linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ia)



15

wherein

D is O or S; and

E is O, S, NR⁵, C(R⁵)₂, O-CR⁵₂, NR⁵-CR⁵₂, NR⁵-CO, CR⁵₂-O, CR⁵₂-S(O)_r, CR⁵₂-NR⁵, CR⁵₂-CR⁵₂, CO-NR⁵, or CR⁵=CR⁵;

unless X is N in which case R² is absent

20

R³ is H, halogen, C₁₋₄alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF₃, OC₁₋₄alkyl, aryloxy, arylC₁₋₄alkyl, arylC₁₋₄alkoxy, C₃₋₁₀cycloalkoxy, carboxy, carbonamido, -CO-, -CO₂H, -NH₂, NH-C₁₋₄alkyl, aryl, hydroxy, -SO₂NH₂, -SO₂NHC₁₋₄alkyl, or -C₁₋₄alkyl-OH;

25

R⁴ is H, halogen, C₁₋₄alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF₃, OC₁₋₄alkyl, aryloxy, arylC₁₋₄alkyl, arylC₁₋₄alkoxy, C₃₋₁₀cycloalkoxy, carboxy, carbonamido, -CO-, -CO₂H, -NH₂, NH-C₁₋₄alkyl, aryl, hydroxy, -SO₂NH₂, -SO₂NHC₁₋₄alkyl, or -C₁₋₄alkyl-OH;

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- R⁵ is each independently H or C₁₋₄alkyl;
X is C or N;
W is C or N;
W' is C or N;
5 Y is C or N;
Y' is C or N;
provided that there are no more than two N atoms in the aryl ring;
m is 1, 2, or 3;
n is 1, 2, or 3; and
10 the sum of m and n is 2, 3, 4, 5, or 6;
provided that
when X, W, W', Y and Y' are all C and R³ and R⁴ are H, R² may not be -OH;
and that
when one of X, Y and Y' is N and R³ and R⁴ are H, R² may not be H;
15 and that
when R² is H, OH or NH₂ and R³ and R⁴ are H, R¹ may not be aryl-C₁₋₄alkyl.
4. The method of any one of claims 1 to 3 wherein
R¹ is -H, or
20 C₁₋₁₂alkyl optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxyl, thiol, C₁₋₄alkoxy or C₁₋₄alkylthio.
5. The method of any one of claims 1 to 4, wherein
R² is -H,
25 -C(O)-NH₂,
-NH₂,
-NH-Q-V-T as defined in claim 1; or
linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ia) as defined in claim 1;
30 unless X is N in which case R² is absent.
6. The method of any one of claims 1 to 5, wherein

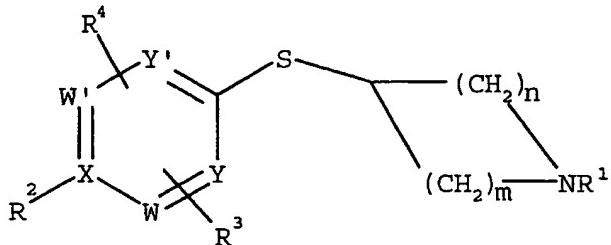
R^2 is $-C(O)-NH_2$,
 $-NH-Q-V-T$ as defined in claim 1; or
linked back to the aromatic ring so as to form a fused bicyclic compound
represented by Formula (Ia) as defined in claim 1;
5 unless X is N in which case R^2 is absent.

7. The method of any one of claims 1 to 6, wherein

R^2 is $-C(O)-NH_2$,
 $-NH-Q-V-T$, wherein Q is $-C(O)-NH-$, or $-C(O)O-$;
10 V is as defined in claim 1; and
 T is as defined in claim 1; or
linked back to the aromatic ring so as to form a fused bicyclic compound
represented by Formula (Ia) as defined in claim 1;
unless X is N in which case R^2 is absent.

15

8. A compound of Formula (I) or pharmaceutically acceptable salts thereof for use in therapy:



(I)

20 wherein:

R^1 is $-H$,
 C_{1-12} alkyl optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxyl, thiol, C_{1-4} alkoxy or C_{1-4} alkylthio, or aryl- $C1-4$ alkyl;
25 R^2 is $-H$,
 $-OH$,

-C(O)-NH₂,

-NH₂,

-NH-Q-V-T, wherein

Q is -C(O)-, -C(O)-NH-, -C(O)O-, or -SO₂-;

V is H, aryl, aryl-C₁₋₁₂alkyl, diaryl-C₁₋₁₂alkyl,

lactonyl, or C₁₋₁₈alkyl optionally substituted

with halogen, hydroxyl, C₁₋₄alkoxy, -

C(O)OC₁₋₄alkyl, -OC(O)C₁₋₄alkyl, aryl-C₁₋

4alkoxy, aryloxy, or SO₂C₁₋₄alkyl; and

T is H, halogen, C₁₋₅alkyl, C₁₋₄alkoxy, nitro,

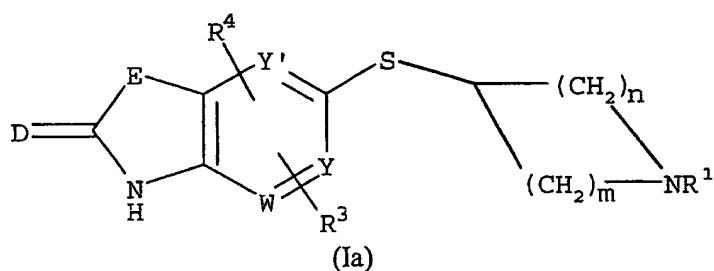
aryl, aryl-C₁₋₄alkyl, or aryloxy unless V is H

in which case T is absent; or

5

10

linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ia)



15

wherein

D is O or S; and

E is O, S, NR⁵, C(R⁵)₂, O-CR⁵₂, NR⁵-CR⁵₂,

NR⁵-CO, CR⁵₂-O, CR⁵₂-S(O)_r, CR⁵₂-NR⁵,

CR⁵₂-CR⁵₂, CO-NR⁵, or CR⁵=CR⁵;

20

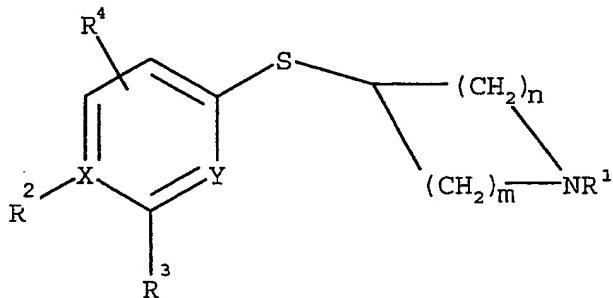
unless X is N in which case R² is absent

R³ is H, halogen, C₁₋₄alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF₃, OC₁₋₄alkyl, aryloxy, arylC₁₋₄alkyl, arylC₁₋₄alkoxy, C₃₋₁₀cycloalkoxy, carboxy, carbonamido, -CO-, -CO₂H, -NH₂, NH-C₁₋₄alkyl, aryl, hydroxy, -SO₂NH₂, -SO₂NHC₁₋₄alkyl, or -C₁₋₄alkyl-OH;

25

R⁴ is H, halogen, C₁₋₄alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF₃, OC₁₋₄alkyl, aryloxy, arylC₁₋₄alkyl, arylC₁₋₄alkoxy, C₃₋₁₀cycloalkoxy, carboxy, carbonamido, -CO-, -CO₂H, -NH₂, NH-C₁₋₄alkyl, aryl, hydroxy, -SO₂NH₂, -SO₂NHC₁₋₄alkyl, or -C₁₋₄alkyl-OH;

R^5 is each independently H or C₁₋₄alkyl;
 X is C or N;
 5 W is C or N;
 W' is C or N;
 Y is C or N;
 Y' is C or N;
 provided that there are no more than two N atoms in the aryl ring;
 10 m is 1, 2, or 3;
 n is 1, 2, or 3; and
 the sum of m and n is 2, 3, 4, 5, or 6;
 provided that
 when X, W, W', Y and Y' are all C and R³ and R⁴ are H, R² may not be -OH;
 15 and that
 when one of X, Y and Y' is N and R³ and R⁴ are H, R² may not be H;
 and that
 when R² is H, OH or NH₂ and R³ and R⁴ are H, R¹ may not be aryl-C₁₋₄alkyl;
 and excluding compounds represented by Formula I' or pharmaceutically acceptable salts
 20 thereof:



(I')

wherein:
 R¹, X, Y, m and n are as defined above
 25 R² is -H,

-NH₂,

-NH-SO₂-V-T wherein V and T are as defined above;

unless X is N in which case R^2 is absent

R^3 is H, halogen, C_{1-4} alkyl, $-NH_2$, $NH-C_{1-4}$ alkyl, or hydroxy;

R⁴ is H, halogen, C₁₋₄alkyl, -NH₂, NH-C₁₋₄alkyl, or hydroxy.

9. A compound as claimed in claim 8 wherein

R' is -H, or

C₁₋₁₂alkyl optionally substituted with 1, 2 or 3 groups independently

selected from halogen, hydroxyl, thiol, C₁₋₄alkoxy or C₁₋₄alkylthio.

10. A compound as claimed in claim 8 or claim 9, wherein

R^2 is -H,

-C(O)-NH₂,

15 -NH₂,

-NH-Q-V-T as defined in claim 8; or

linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ia) as defined in claim 8;

unless X is N in which case R² is absent.

20

11. A compound as claimed in any one of claims 8 to 10, wherein

R^2 is $-C(O)-NH_2$,

-NH-Q-V-T as defined in claim 8; or

linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ia) as defined in claim 8;

represented by Formula (Ia) as defined in claim 8:

unless X is N in which case R² is absent.

12. A compound as claimed in any one of claims 8 to 11, wherein

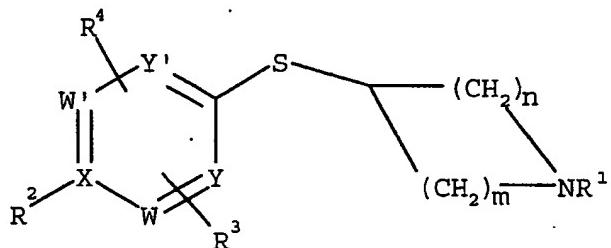
R^2 is $-C(O)-NH_2$,

30 -NH-Q-V-T, wherein Q is -C(O)-NH-, or -C(O)O-; V is as defined in claim 8; and T is as defined in claim 8; or

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linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ia) as defined in claim 8; unless X is N in which case R² is absent.

- 5 13. A compound represented by Formula (I) or pharmaceutically acceptable salts thereof:



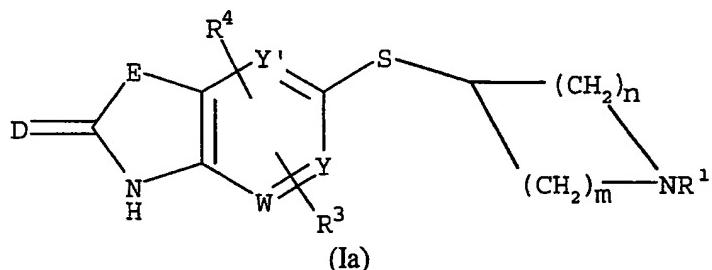
(I)

wherein:

- 10 R¹ is -H,
C₁₋₁₂alkyl optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxyl, thiol, C₁₋₄alkoxy or C₁₋₄alkylthio, or aryl-C₁₋₄alkyl;
- 15 R² is -H,
-OH,
-C(O)-NH₂,
-NH₂,
-NH-Q-V-T, wherein Q is -C(O)-, -C(O)-NH-, -C(O)O-, or -SO₂-; V is H, aryl, aryl-C₁₋₁₂alkyl, diaryl-C₁₋₁₂alkyl, lactonyl, or C₁₋₁₈alkyl optionally substituted with halogen, hydroxyl, C₁₋₄alkoxy, -C(O)OC₁₋₄alkyl, -OC(O)C₁₋₄alkyl, aryl-C₁₋₄alkoxy, aryloxy, or SO₂C₁₋₄alkyl; and T is H, halogen, C₁₋₅alkyl, C₁₋₄alkoxy, nitro, aryl, aryl-C₁₋₄alkyl, or aryloxy unless V is H in which case T is absent; or
- 20
- 25

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linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ia)



5 wherein D is O or S; and ;
E is O, S, NR⁵, C(R⁵)₂, O-CR⁵₂, NR⁵-CR⁵₂,
NR⁵-CO, CR⁵₂-O, CR⁵₂-S(O)_r, CR⁵₂-NR⁵,
CR⁵₂-CR⁵₂, CO-NR⁵, or CR⁵=CR⁵;

unless X is N in which case R^2 is absent

10 R³ is H, halogen, C₁₋₄alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF₃, OC₁₋₄alkyl, aryloxy, arylC₁₋₄alkyl, arylC₁₋₄alkoxy, C₃₋₁₀cycloalkoxy, carboxy, carbonamido, -CO-, -CO₂H, -NH₂, NH-C₁₋₄alkyl, aryl, hydroxy, -SO₂NH₂, -SO₂NHC₁₋₄alkyl, or -C₁₋₄alkyl-OH;

R^4 is H, halogen, C₁₋₄alkyl optionally substituted with from 1 to 3 fluorine

15 atoms, cyano, CF_3 , $\text{OC}_1\text{-}4\text{alkyl}$, aryloxy, aryl $\text{C}_1\text{-}4\text{alkyl}$, aryl $\text{C}_1\text{-}4\text{alkoxy}$, $\text{C}_{3-10}\text{cycloalkoxy}$, carboxy, carbonamido, -CO-, -CO₂H, -NH₂, NH-C₁₋₄alkyl, aryl, hydroxy, -SO₂NH₂, -SO₂NHC₁₋₄alkyl, or -C₁₋₄alkyl-OH;

R^5 is each independently H or C_{1-4} alkyl;

X is C or N:

20 W is C or N:

W' is C or N.

Y is C or N.

V' is C or N.

provided that there are no more than two N atoms in the aryl ring;

35 m is 1, 2, or 3:

n is 1, 2, or 3; and

the sum of m and n is 2, 3, 4, 5, or 6;

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provided that

when X, W, W', Y and Y' are all C and R³ and R⁴ are H, R² may not be -OH;

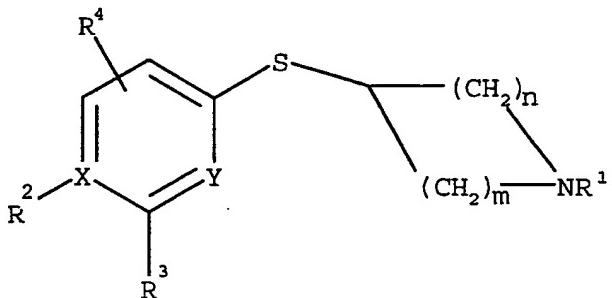
and that

when one of X, Y and Y' is N and R³ and R⁴ are H, R² may not be H;

5 and that

when R² is H, OH or NH₂ and R³ and R⁴ are H, R¹ may not be aryl-C1-4alkyl;

and excluding compounds represented by Formula I'' or pharmaceutically acceptable salts thereof:



10

(I'')

wherein:

R¹, X, Y, m and n are as defined above

R² is -H,

-NH₂,

15

-NH-Q-V-T, wherein Q is -C(O)- or -SO₂- and

V and T are as defined above;

unless X is N in which case R² is absent

R³ is H, halogen, C₁₋₄alkyl, OC₁₋₄alkyl, -NH₂, NH-C₁₋₄alkyl, or hydroxy;

R⁴ is H, halogen, C₁₋₄alkyl, OC₁₋₄alkyl, CO₂H, -NH₂, NH-C₁₋₄alkyl, or hydroxy.

20

14. A compound as claimed in claim 13 wherein

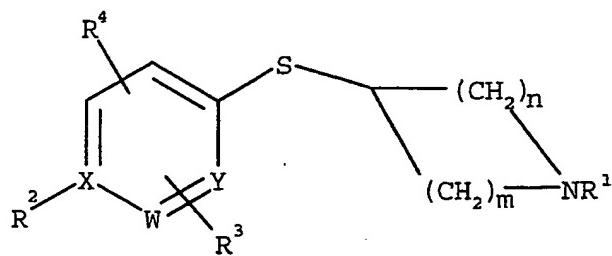
R¹ is -H, or

C₁₋₁₂alkyl optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxyl, thiol, C₁₋₄alkoxy or C₁₋₄alkylthio.

25

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15. A compound as claimed in claim 13 or claim 14, wherein
R² is -H,
-C(O)-NH₂,
-NH₂,
5 -NH-Q-V-T as defined in claim 13; or
linked back to the aromatic ring so as to form a fused bicyclic compound
represented by Formula (Ia) as defined in claim 13;
unless X is N in which case R² is absent.
- 10 16. A compound as claimed in any one of claims 13 to 15, wherein
R² is -C(O)-NH₂,
-NH-Q-V-T as defined in claim 13; or
linked back to the aromatic ring so as to form a fused bicyclic compound
represented by Formula (Ia) as defined in claim 13;
15 unless X is N in which case R² is absent.
17. A compound as claimed in any one of claims 13 to 16, wherein
R² is -C(O)-NH₂,
-NH-Q-V-T, wherein Q is -C(O)-NH-, or -C(O)O-;
20 V is as defined in claim 13; and
T is as defined in claim 13; or
linked back to the aromatic ring so as to form a fused bicyclic compound
represented by Formula (Ia) as defined in claim 13;
unless X is N in which case R² is absent.
- 25 18. A compound as claimed in claim 13 which is represented by Formula (II) or
pharmaceutically acceptable salts thereof:



wherein:

- R^1 is $-H$; or
- 5 C_{1-12} alkyl optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxyl, thiol, C_{1-4} alkoxy or C_{1-4} alkylthio; or aryl- C_{1-4} alkyl;
- R^2 is $-H$;
- 10 $-OH$;
- $-C(O)-NH_2$
- $-NH_2$;
- $-NH-Q-V-T$
- Q is $-C(O)-$;
- 15 $-C(O)-NH-$;
- $-C(O)O-$; or
- $-SO_2-$
- V is aryl;
- aryl- C_{1-12} alkyl;
- diaryl- C_{1-12} alkyl;
- 20 lactonyl; or
- C_{1-18} alkyl optionally substituted with halogen, hydroxyl, C_{1-4} alkoxy, $-C(O)OC_{1-4}$ alkyl, $-OC(O)C_{1-4}$ alkyl, aryl- C_{1-4} alkoxy, aryloxy, SO_2C_{1-4} alkyl;
- T is H ;
- halogen;
- 25 aryl;
- aryl- C_{1-4} alkyl; or
- aryloxy;

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unless X is N in which case R² is absent

R³ and R⁴ are each independently selected from H, halogen, C₁₋₄ alkyl, cyano, CF₃, OC₁₋₄ alkyl, aryloxy, arylC₁₋₄alkoxy, C₃₋₁₀ cycloalkoxy, carboxy, carbonamido, -CO-, -CO₂H, -NH₂, NH-C₁₋₄ alkyl, aryl, hydroxy, -SO₂NH₂, -SO₂NHC₁₋₄

5 alkyl, -C₁₋₄ alkyl-OH;

X is C or N;

W is C or N, provided that both X and Y are not N;

Y is C or N

m is 1, 2, or 3;

10 n is 1, 2, or 3; and

the sum of m and n is 2, 3, 4, 5, or 6.

19. A compound as claimed in claim 18 wherein R¹ is H; C₁₋₆ alkyl optionally substituted with 1 or 2 hydroxyl groups; or aryl-C₁₋₄ alkyl.

15

20. A compound as claimed in claim 19 wherein R¹ is benzyl, p-methoxybenzyl, furanylmethyl, imidazolylmethyl, pyridinylmethyl, thienylmethyl, pyridylmethyl, N-hydroxypyridylmethyl or thiazolylmethyl.

20

21. A compound as claimed in any one of claims 18 to 20 wherein R² is H, R³ is carbonamido (-CONH₂) or C₁₋₄ alkyl-OH, and R⁴ is H, C₁₋₄alkyl, CF₃, halogen or cyano.

22. A compound as claimed in any one of claims 18 to 20 wherein R² is OH, and R³ and R⁴ each independently represent H, C₁₋₄alkyl, CF₃, cyano or halogen.

25

23. A compound as claimed in any one of claims 18 to 20 wherein R² is of formula - NH-Q-V-T; T is H and R³ and R⁴ each independently represent H, methyl, CF₃, chloro- or cyano-.

30

24. A compound as claimed in any one of claims 18 to 20 wherein R² is of formula - NH-SO₂-V-T; V is aryl, -C₁₋₁₂ alkyl or aryl-C₁₋₁₂ alkyl; R₃ is H, methyl, CF₃, Cl or cyano and R⁴ is H.

25. A compound as claimed in any one of claims 18 to 20 wherein R² is of formula – NH-SO₂-V-T, V is selected from C₁₋₁₂ alkyl, phenyl, naphthyl, thiaryl, oxazolyl, isoxazolyl, or phenyl(CH=CH)–, optionally substituted with 1, 2, 3 or 4 substituents
5 selected from:
- NO₂;
halogen;
-CF₃;
C₁₋₁₂ alkoxy;
10 C₁₋₁₂ alkylthio;
C₁₋₁₂ alkyl;
C₁₋₄ alkylsulfonyl;
-CN;
-OCF₃;
15 -C(O)OC₁₋₄ alkyl;
-OCH₂CF₃;
-NHC(O) C₁₋₄ alkyl.
26. A compound as claimed in any one of claims 18 to 20 wherein R² is of formula – NH-SO₂-V-T, T is selected from H; or diazole, oxazole, isoxazole, phenyl or phenoxy, optionally substituted with 1, 2, 3 or 4 substituents selected from
20
-NO₂;
halogen;
-CF₃;
C₁₋₁₂ alkoxy;
25 C₁₋₁₂ alkylthio;
C₁₋₁₂ alkyl;
C₁₋₄ alkylsulfonyl;
-CN;
30 -OCF₃;
-C(O)OC₁₋₄ alkyl;
-OCH₂CF₃;

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-NHC(O) C₁₋₄ alkyl.

27. A compound as claimed in any one of claims 18 to 20 wherein R² is of formula – NH-SO₂-V-T, V is selected from 3-chloro-4-methylphenyl, 3-chlorophenyl, 3-methoxyphenyl, 4-bromophenyl, 4-methoxyphenyl, 4-methylphenyl, naphthyl, 2,4,6-trimethylphenyl, phenyl(CH=CH)-, 4-chlorophenyl, 2-chlorophenyl, 2,5-dichlorothien-3-yl, 2,5,6-trimethyl-4-methoxyphenyl, 4-methoxyphenyl, 2,3,4-trifluorophenyl, 3-cyanophenyl, 2-methoxycarbonylthien-3-yl or 4-pentylphenyl and T is H.
- 10 28. A compound as claimed in any one of claims 18 to 20 wherein R² is of formula – NH-SO₂-V-T, T is 2-chloro-5-nitrophenoxy and V is phenyl.
29. A compound as claimed in any one of claims 18 to 20 wherein R² is of formula – NH-C(O)-V-T wherein V is selected from
- 15 aryl;
aryl-C₁₋₁₂ alkyl;
 diaryl-C₁₋₁₂ alkyl;
 lactonyl; or
C₁₋₁₈ alkyl optionally substituted with halogen, hydroxyl, C₁₋₄
- 20 alkoxy, C(O)OC₁₋₄ alkyl, OC(O)C₁₋₄ alkyl, aryl-C₁₋₄ alkoxy, aryloxy.
30. A compound as claimed in any one of claims 18 to 20 wherein R² is of formula – NH-C(O)-V-T, and V is selected from C₁₋₁₂ alkyl, phenyl, phenyl-C₁₋₁₂ alkyl, diphenylmethyl, naphthyl, furanyl, thieryl, diazolyl, pyridinyl, thiazolyl, benzothienyl, fluorenly, oxazolyl or isoxazolyl, optionally substituted with 1, 2, 3 or 4 substituents independently selected from
- NO₂;
halogen;
-CF₃;
- 30 C₁₋₁₂ alkoxy;
C₁₋₁₂ alkylthio;
C₁₋₁₂ alkyl;
C₁₋₄ alkylsulfonyl;

-CN;
-OCF₃;
-C(O)O-C₁₋₄ alkyl;
-OCH₂CF₃.

5

31. A compound as claimed in any one of claims 18 to 20 wherein R² is of formula – NH-C(O)-V-T, T is selected from

H;

halogen; or

10 diazole, oxazole, isoxazole, phenyl, phenoxy or benzodioxanyl optionally substituted with 1, 2, 3 or 4 substituents selected from

-NO₂;

halogen;

-CF₃;

15 C₁₋₁₂ alkylthio;

C₁₋₁₂ alkoxy;

C₁₋₁₂ alkyl;

C₁₋₄ alkylsulfonyl;

-CN;

20 -OCF₃;

-C(O)O-C₁₋₄ alkyl.

32. A compound as claimed in any one of Claims 18 to 20 wherein R² is of formula – NH-C(O)N-V-T wherein V is selected from

25 C₁₋₁₈ alkyl optionally substituted with halogen, hydroxyl, C₁₋₄ alkoxy, C(O)OC₁₋₄ alkyl, OC(O)C₁₋₄ alkyl, aryl-C₁₋₄ alkoxy, aryloxy; aryl; or aryl-C₁₋₁₂ alkyl.

30 33. A compound as claimed in any one of claims 18 to 20 wherein R² is of formula – NH-C(O)NH-V-T, V is selected from phenyl, phenyl-C₁₋₁₂ alkyl or naphthyl optionally substituted with 1, 2, 3 or 4 substituents selected from

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- NO₂;
- halogen;
- CF₃;
- C₁₋₁₂ alkylthio;
- 5 C₁₋₁₂ alkoxy;
- C₁₋₁₂ alkyl;
- C₁₋₄ alkylsulfonyl;
- CN;
- OCF₃;
- 10 -C(O)O-C₁₋₄ alkyl.

34. A compound as claimed in any one of claims 18 to 20 wherein R² is of formula – NH-C(O)O-V-T, wherein V is selected from

- C₁₋₁₈ alkyl optionally substituted with halogen, hydroxyl, C₁₋₄ alkoxy,
- 15 C(O)OC₁₋₄ alkyl, OC(O)C₁₋₄ alkyl, aryl-C₁₋₄ alkoxy, aryloxy;
- aryl; or
- aryl-C₁₋₁₂ alkyl.

35. A compound as claimed in any one of claims 18 to 20 wherein R² is of formula – NH-C(O)O-V-T, preferably V is selected from phenyl or phenyl-C₁₋₁₂ alkyl optionally substituted with 1, 2, 3 or 4 substituents selected from

- NO₂;
- halogen;
- CF₃;
- 25 C₁₋₁₂ alkylthio;
- C₁₋₁₂ alkoxy;
- C₁₋₁₂ alkyl;
- C₁₋₄ alkylsulfonyl;
- CN;
- 30 -OCF₃;
- C(O)O-C₁₋₄ alkyl; or
- OCH₂CF₃.

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36. A compound as claimed in claim 13 wherein R² is of formula -NH-C(O)-V-T
wherein V is H, C₁₋₆alkyl, C₃₋₆cycloalkyl, aryl or aryl-C₁₋₁₂alkyl; and
T is H, halogen, C₁₋₅alkyl, C₁₋₄alkoxy, nitro, aryl, aryl-C₁₋₄alkyl, or aryloxy
unless V is H in which case T is absent.

5

37. A compound as claimed in claim 36
wherein V is H, C₁₋₆alkyl or C₃₋₆cycloalkyl, and
T is H unless V is H in which case T is absent.

10 38. A compound as claimed in claim 36
wherein V is aryl or aryl-C₁₋₁₂alkyl, and
T is H, halogen, C₁₋₅alkyl, C₁₋₄alkoxy, nitro, aryl, aryl-C₁₋₄alkyl, or aryloxy.

15 39. A compound as claimed in claim 38
wherein V is phenyl, pyridyl, thienyl, thiazolyl, thiadiazolyl, or phenyl-C₁₋₆alkyl;
and
T is H, halogen, C₁₋₅alkyl, C₁₋₄alkoxy, nitro, aryl, aryl-C₁₋₄alkyl, or aryloxy.

20 40. A compound as claimed in claim 13
wherein
R¹ is -H,
C₁₋₁₂alkyl optionally substituted with 1, 2 or 3 groups independently
selected from halogen, hydroxyl, thiol, C₁₋₄alkoxy or C₁₋₄alkylthio, or
aryl-C₁₋₄alkyl;
25 R² is -NH₂, or
-NH-Q-V-T, wherein Q is -C(O)-, -C(O)-NH-, -C(O)O-, or -SO₂-;
V is H, aryl, aryl-C₁₋₁₂alkyl, diaryl-C₁₋₁₂alkyl,
lactonyl, or C₁₋₁₈alkyl optionally substituted
with halogen, hydroxyl, C₁₋₄alkoxy, -
C(O)OC₁₋₄alkyl, -OC(O)C₁₋₄alkyl, aryl-C₁₋₄alkoxy, aryloxy, or SO₂C₁₋₄alkyl; and
30

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T is H, halogen, aryl, aryl-C₁₋₄alkyl, or aryloxy unless V is H in which case T is absent,

- 5 R³ is H, halogen, C₁₋₄alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF₃, OC₁₋₄alkyl, aryloxy, arylC₁₋₄alkyl, arylC₁₋₄alkoxy, C₃₋₁₀cycloalkoxy, carboxy, carbonamido, -CO-NH-C₁₋₄alkyl, aryl, hydroxy, -SO₂NH₂, -SO₂NHC₁₋₄alkyl, or -C₁₋₄alkyl-OH;
- 10 R⁴ is H, halogen, C₁₋₄alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF₃, OC₁₋₄alkyl, aryloxy, arylC₁₋₄alkyl, arylC₁₋₄alkoxy, C₃₋₁₀cycloalkoxy, carboxy, carbonamido, -CO-NH-C₁₋₄alkyl, aryl, hydroxy, -SO₂NH₂, -SO₂NHC₁₋₄alkyl, or -C₁₋₄alkyl-OH;
- 15 X is C;
W is C or N;
W' is C or N;
Y is C or N;
Y' is C or N;
- provided that there are not more than two N atoms in the aryl ring and provided that at least one of W, W', Y or Y' is N;
- 20 m is 1, 2, or 3;
n is 1, 2, or 3; and
the sum of m and n is 2, 3, 4, 5, or 6.

41. A compound as claimed in claim 40

wherein

- 25 W is C;
W' is C;
Y' is C; and
Y is N.

30 42. A compound as claimed in claim 40

wherein

- W is N;

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W' is C;
Y' is C; and
Y is C.

- 5 43. A compound as claimed in any one of claims 40 to 42
wherein

R^2 is -NH₂.

- 10 44. A compound as claimed in any one of claims 40 to 42
wherein

R^2 is -NH-Q-V-T, wherein Q is -C(O)-, -C(O)-NH-, -C(O)O-, or -SO₂-;
V is H, aryl, aryl-C₁₋₁₂alkyl, diaryl-C₁₋₁₂alkyl,
lactonyl, or C₁₋₁₈alkyl optionally substituted
with halogen, hydroxyl, C₁₋₄alkoxy, -
15 C(O)OC₁₋₄alkyl, -OC(O)C₁₋₄alkyl, aryl-C₁₋₄alkoxy, aryloxy, or SO₂C₁₋₄alkyl; and
T is H, halogen, aryl, aryl-C₁₋₄alkyl, or
aryloxy unless V is H in which case T is
absent.

- 20 45. A compound as claimed in claim 44
wherein

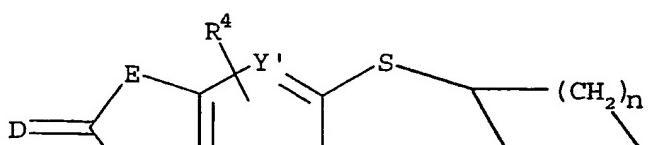
Q is -SO₂- or -CO-.

- 25 46. A compound as claimed in Claim 13
wherein:

R^1 is -H,

C₁₋₁₂alkyl optionally substituted with 1, 2 or 3 groups independently
selected from halogen, hydroxyl, thiol, C₁₋₄alkoxy or C₁₋₄alkylthio, or
30 aryl-C₁₋₄alkyl;

R^2 is linked back to the aromatic ring so as to form a fused bicyclic compound



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represented by Formula (Ia)

(Ia)

wherein D is O or S; and

E is O, S, NR⁵, or C(R⁵)₂,

5 R³ is H, halogen, C₁₋₄alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF₃, OC₁₋₄alkyl, aryloxy, arylC₁₋₄alkyl, arylC₁₋₄alkoxy, C₃₋₁₀cycloalkoxy, carboxy, carbonamido, -CO-NH-C₁₋₄alkyl, aryl, hydroxy, -SO₂NH₂, -SO₂NHC₁₋₄alkyl, or -C₁₋₄alkyl-OH;

10 R⁴ is H, halogen, C₁₋₄alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF₃, OC₁₋₄alkyl, aryloxy, arylC₁₋₄alkyl, arylC₁₋₄alkoxy, C₃₋₁₀cycloalkoxy, carboxy, carbonamido, -CO-NH-C₁₋₄alkyl, aryl, hydroxy, -SO₂NH₂, -SO₂NHC₁₋₄alkyl, or -C₁₋₄alkyl-OH;

15 R⁵ is each independently H or C₁₋₄alkyl;

 X is C;

 W is C or N;

 W' is C;

 Y is C or N;

 Y' is C or N;

20 provided that there are no more than two N atoms in the aryl ring,

 m is 1, 2, or 3;

 n is 1, 2, or 3; and

 the sum of m and n is 2, 3, 4, 5, or 6.

25 47. A compound as claimed in Claim 46 wherein E is O or NR⁵.

48. A compound as claimed in Claim 46 or 47 wherein R⁵ is/are each independently H or C₁₋₄alkyl.

30 49. A compound as claimed in Claim 13

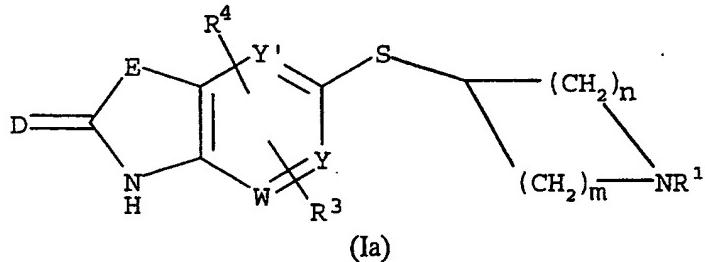
wherein:

 R¹ is -H,

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C_{1-12} alkyl optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxyl, thiol, C_{1-4} alkoxy or C_{1-4} alkylthio, or aryl- C_{1-4} alkyl;

5 R^2 is linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ia)



wherein D is O or S; and

10 E is $O-CR^5_2$, $NR^5-CR^5_2$, NR^5-CO , CR^5_2-O ,
 $CR^5_2-S(O)_r$, $CR^5_2-NR^5$, $CR^5_2-CR^5_2$, $CO-NR^5$,
 NR^5 , or $CR^5=CR^5$;

15 R^3 is H, halogen, C_{1-4} alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF_3 , OC_{1-4} alkyl, aryloxy, aryl C_{1-4} alkyl, aryl C_{1-4} alkoxy, C_{3-10} cycloalkoxy, carboxy, carbonamido, -CO-NH- C_{1-4} alkyl, aryl, hydroxy, - SO_2NH_2 , - SO_2NHC_{1-4} alkyl, or - C_{1-4} alkyl-OH;

20 R^4 is H, halogen, C_{1-4} alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF_3 , OC_{1-4} alkyl, aryloxy, aryl C_{1-4} alkyl, aryl C_{1-4} alkoxy, C_{3-10} cycloalkoxy, carboxy, carbonamido, -CO-NH- C_{1-4} alkyl, aryl, hydroxy, - SO_2NH_2 , - SO_2NHC_{1-4} alkyl, or - C_{1-4} alkyl-OH;

25 R^5 is each independently H, C_{1-4} alkyl;

X is C;

W is C or N;

W' is C;

Y is C or N;

Y' is C or N;

provided that there are no more than two N atoms in the aryl ring;

m is 1, 2, or 3;

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n is 1, 2, or 3; and
the sum of m and n is 2, 3, 4, 5, or 6.

50. A compound as claimed in Claim 49 wherein E is O-CR⁵₂, NR⁵-CR⁵₂, NR⁵-CO,
5 CR⁵₂-CR⁵₂, or CR⁵=CR⁵.

51. A compound as claimed in Claim 49 or 50 wherein E is O-CR⁵₂, NR⁵-CO, or
CR⁵=CR⁵.

10 52. A compound as claimed in any one of Claims 49 to 51 wherein R⁵ is/are each
independently H or C₁₋₄alkyl.

53. A compound as claimed in any one of claims 18 to 35 wherein m is 2 and n is 1, 2
or 3.

15 54. A compound as claimed in any one of claims 18 to 35 wherein m is 2 and n is 2.

55. A compound as claimed in any one of claims 18 to 35 wherein X, Y and W are C.

20 56. A compound as claimed in any preceding claim wherein R¹ is H or C₁₋₃alkyl.

57. A pharmaceutical composition comprising a compound as claimed in any one of
claims 8 to 56 with a pharmaceutically acceptable diluent or carrier.

INTERNATIONAL SEARCH REPORT

Inte	al Application No
PCT/US 02/21297	

A. CLASSIFICATION OF SUBJECT MATTER					
IPC 7	C07D401/12	C07D211/54	C07D207/12	C07D223/06	A61K31/4465

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 01 81303 A (HOFFMANN LA ROCHE) 1 November 2001 (2001-11-01) see Scheme 15, compounds 1-15; Scheme 16, compounds 1-16 page 1, line 1 -page 2, line 29; examples 40,56,67,68,91 ---	1-7, 18-35, 40-57
X	WO 01 51469 A (ACKERMANN KARL AUGUST ;AMSTERDAM CHRISTOPH VAN (DE); BOETTCHER HEN) 19 July 2001 (2001-07-19) page 1, line 1 -page 4, line 5; example 2 ---	1-7, 18-35, 40-57
X	US 6 124 323 A (BIGGE CHRISTOPHER F ET AL) 26 September 2000 (2000-09-26) column 10, line 15 -column 12, line 34 --- -/-	1-7, 18-35, 40-57

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

• Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the International filing date but later than the priority date claimed

- *T* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the International search	Date of mailing of the International search report
11 November 2002	26/11/2002
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel: (+31-70) 340-2040, Tx: 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Usuelli, A

INTERNATIONAL SEARCH REPORT

Inte	d Application No
PCT/US 02/21297	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 705 853 A (CALE JR ALBERT D) 10 November 1987 (1987-11-10) Preparation 22 column 37 ---	18
X	DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; WANG, H.; WEN, R.; HUANG, L.; INNIS, R.B.; TAN, P.: "Synthesis and biological activities of new 5-HT2A selective ligands N-substituted-piperidinyl-4-phenylthioether and sulfone derivatives" retrieved from STN, accession no. 2001: 425735 Database accession no. 136:247481 XP002220125 RNs: 403848-69-1 and 403848-67-9 abstract -----	18

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 8-17, 36-45, 56 (part), 57 (part)

Present claims 8-57 relate to an extremely large number of possible compounds and compositions. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, claims 8-57 so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of claims 18 (Formula II), 46 and 49.

The subject matter of claims 1-7 has been searched completely.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/21297

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-7 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.
2. Claims Nos.: 8-17, 36-45, 56 (part), 57 (part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte
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PCT/US 02/21297

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Intell	ai Application No
PCT/US 02/21297	

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